

## **Supporting Information**

### **Ladder Polyether Synthesis *via* Epoxide-Opening Cascades Using A Disappearing Directing Group**

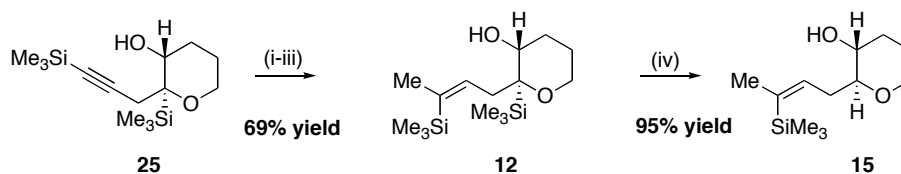
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<b>Schematic Summary of Synthetic Operations</b>	<b>S2</b>
<b>Experimental Procedures and Data for Compounds 1-26.</b>	<b>S4-S78</b>

## Schematic Summary of Synthetic Operations

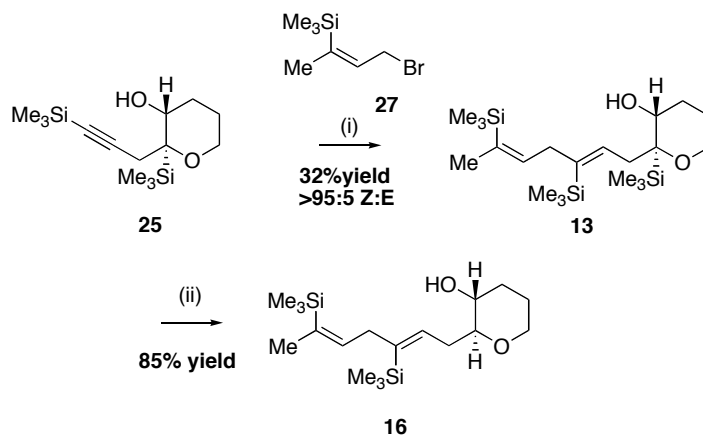
### Preparation of olefins 12 and 15



**Scheme 1**

**Reagents and conditions:** (i) DIBAL (300 mol%), Et<sub>2</sub>O, reflux, 20h; (ii) MeLi (300 mol%); CuCN•2LiCl (100 mol%), THF (iii) MeI (400 mol%), THF; (iv) TBAF (1M in THF), THF, 40°C.

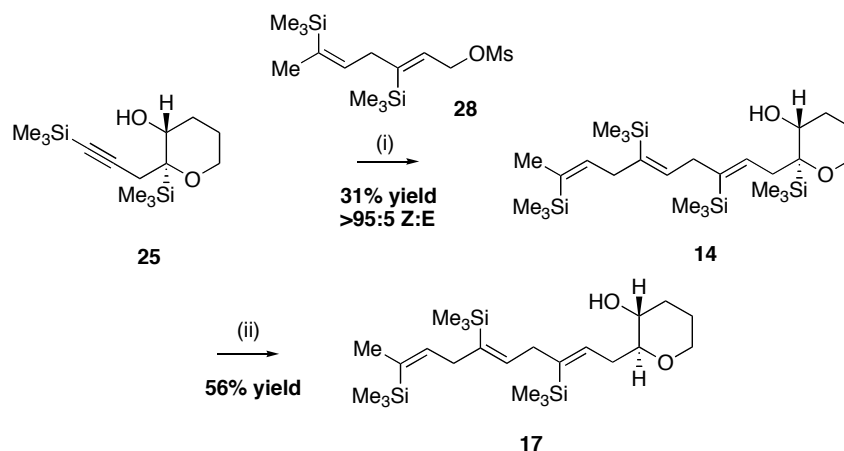
### Preparation of dienes 13 and 16



**Scheme 2**

**Reagents and conditions:** (i) Cp<sub>2</sub>ZrHCl (350 mol%), THF; MeLi (110 mol%), Et<sub>2</sub>O; Me<sub>2</sub>CuCNLi<sub>2</sub> (110 mol%), Et<sub>2</sub>O; bromide 27 (400 mol%), THF; (ii) TBAF (1M in THF), THF, 40°C.

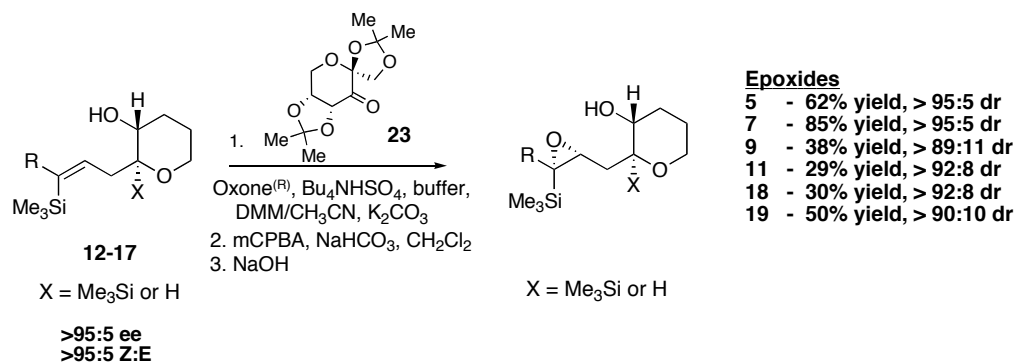
## Preparation of trienes 14 and 17



**Scheme 3**

**Reagents and conditions:** (i) DIBAL (350 mol%), Et<sub>2</sub>O; MeLi (110 mol%), Et<sub>2</sub>O; CuI•P(OEt)<sub>3</sub> (110 mol%), Et<sub>2</sub>O; mesylate **27** (200 mol%), THF; (ii) TBAF (1M in THF), THF, 40°C.

## General Scheme - Shi Epoxidation



**Scheme 4**

In all cases, epoxides **5-19** could not be separated from the excess Shi ketone **23** still present in the crude reaction mixture. Treatment with *m*-CPBA (150 mol%), NaHCO<sub>3</sub> (500 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (0.2M) for 30 min - 2 h followed by NaOH (1.0 M) workup gave the crude epoxide that was purified by silica gel chromatography.

## Experimental Procedures and Data for Compounds 1-26.

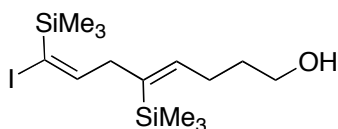
**General Information.** Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and Et<sub>2</sub>O were distilled from a blue solution of benzophenone ketyl. Schwartz's reagent (Cp<sub>2</sub>ZrHCl) was prepared according to the procedure of Buchwald.<sup>1</sup> CuI•P(OEt)<sub>3</sub> was prepared according to the method of Nishizawa and stored in a desiccators in the absence of light.<sup>2</sup> Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F<sub>254</sub> plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA), ceric ammonium molybdate (CAM), vanillin or aqueous potassium permanganate (KMnO<sub>4</sub>). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).<sup>3</sup> <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub>, unless otherwise noted, on a Varian Inova 500 MHz spectrometer, a Bruker Avance 400 MHz spectrometer or a Bruker Avance 600 MHz spectrometer. Chemical shifts in <sup>1</sup>H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or CD<sub>2</sub>Cl<sub>2</sub> (5.30 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 <sup>13</sup>C NMR spectra are reported in ppm from the central peak of CDCl<sub>3</sub> (77.2 ppm), C<sub>6</sub>D<sub>6</sub> (128.4 ppm), or CD<sub>2</sub>Cl<sub>2</sub> (54.0 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.

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<sup>1</sup> Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth., Coll. Vol. IX* **1998**, 162.

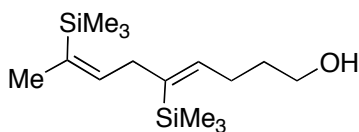
<sup>2</sup> Nishizawa, Y. *Bull. Chem. Soc. Jpn.* **1961**, 34, 1170.

<sup>3</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.



**21**

**(4Z,7E)-8-Iodo-5,8-bis-trimethylsilanyl-octa-4,7-dien-1-ol (21):** To a solution of (4Z)-5,8-Bis-trimethylsilanyl-oct-4-en-7-yn-1-ol<sup>4</sup> (18.7 g, 69.8 mmol) in Et<sub>2</sub>O (170 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (170 mL). The resulting solution was heated 24 h at reflux. The solution was then cooled to –78 °C, diluted with Et<sub>2</sub>O (50 mL), and a solution of I<sub>2</sub> (71.0 g, 279.1 mmol) in Et<sub>2</sub>O (150 mL) was added. After stirring 2 h at –78 °C the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (40 g). The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 200 mL). The combined organic layers were washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **21** (22.9 g, 83%, >95% *E*): R<sub>f</sub> = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2953, 2896, 1614, 1407, 1249, 1057, 839, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.07 (t, *J* = 7.6 Hz, 1H), 5.93 (t, *J* = 7.6 Hz, 1H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.81 (d, *J* = 7.6 Hz, 2H), 2.21 (q, *J* = 14.9, 7.3 Hz, 2H), 1.64 (t, *J* = 7.3 Hz, 2H), 1.42 (s, 1H-OH), 0.25 (s, 9H), 0.15 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.6, 143.3, 137.3, 107.2, 62.7, 42.3, 33.2, 28.6, 1.3, 0.4; HR-MS (ESI) Calcd for C<sub>14</sub>H<sub>29</sub>NaIOSi<sub>2</sub> (M + Na)<sup>+</sup> 419.0694, found 419.0674.

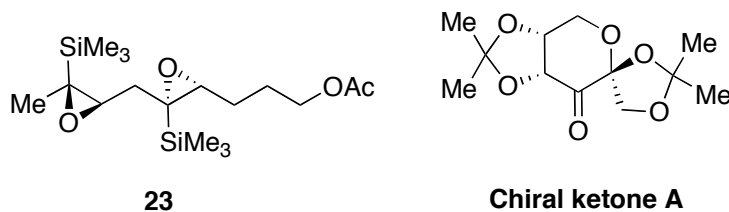


**22**

**(4Z,7Z)-5,8-Bis-trimethylsilanyl-nona-4,7-dien-1-ol (22):** To a slurry of CuCN (2.5 g, 28.4 mmol) in Et<sub>2</sub>O (34.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et<sub>2</sub>O (35.5 mL) and the mixture stirred 15 min. A solution of alkenyl iodide **21** (5.0 g, 12.6 mmol) in Et<sub>2</sub>O (12.8 mL) was slowly added. The reaction was stirred for 20 h at

<sup>4</sup> Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, 5, 2339.

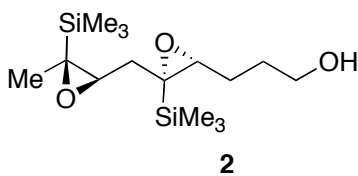
0 °C then was carefully quenched with saturated NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O (3 × 40 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford diene **22** (3.1 g, 86%): R<sub>f</sub> = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3322, 2953, 1615, 1248, 1058, 836, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.95-5.89 (m, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.85-2.82 (m, 2H), 2.21 (app q, *J* = 7.0 Hz, 2H), 1.78 (d, *J* = 2.7 Hz, 3H), 1.67-1.62 (m, 2H), 0.15 (s, 9H), 0.11 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 142.1, 141.5, 139.2, 135.6, 62.9, 39.3, 33.3, 28.7, 24.9, 0.5, 0.0; HR-MS (ESI) Calcd for C<sub>15</sub>H<sub>32</sub>NaOSi<sub>2</sub> (M + Na)<sup>+</sup> 307.1884, found 307.1889.



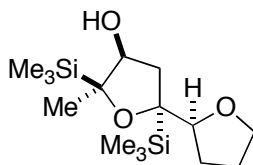
**Acetic acid 3-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propyl ester (**23**):** To a solution of alcohol **22** (2.5 g, 8.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (87 mL) at 0 °C was added pyridine (0.8 g, 10.4 mmol), Ac<sub>2</sub>O (1.1 g, 10.4 mmol), and DMAP (0.11 g, 0.9 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH<sub>4</sub>Cl and concentrated *in vacuo*. The remaining contents were extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) and carried to the next step.

To a solution of the acetate (2.0 g, 6.2 mmol) in CH<sub>3</sub>CN/DMM (192 mL, 1:2 v:v) was added a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (129 mL), *n*-BuNH<sub>2</sub>SO<sub>4</sub> (0.4 g, 1.2 mmol), and chiral ketone **A** (3.2 g, 12.3 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (12.5 g, 20.0 mmol) in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (86.0 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (86.0 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (4 × 400 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and

concentrated *in vacuo*. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford bisepoxide **23** (1.3 g, 42% over 2 steps, dr >95:5):  $R_f = 0.47$  (20% EtOAc in hexane);  $[\alpha]_D^{25} = +3.7$  ( $c = 2.7$ ,  $\text{CHCl}_3$ ); IR (thin film, NaCl) 2958, 1742, 1367, 1250, 1045, 840, 756  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.18-4.09 (m, 2H), 2.87 (dd,  $J = 7.9, 4.9$  Hz, 1H), 2.73 (dd,  $J = 8.2, 3.7$  Hz, 1H), 2.18 (dd,  $J = 14.7, 3.9$  Hz, 1H), 2.05 (s, 3H), 1.92-1.72 (m, 3H), 1.58-1.50 (m, 1H), 1.34 (dd,  $J = 14.6, 8.5$  Hz, 1H), 1.22 (s, 3H), 0.19 (s, 9H), 0.10 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.8, 64.7, 63.7, 62.8, 56.6, 55.5, 38.9, 28.0, 27.0, 23.4, 21.7, -0.5, -1.1; HR-MS (ESI) Calcd for  $\text{C}_{17}\text{H}_{34}\text{O}_4\text{Si}_2$  ( $\text{M} + \text{Na}$ ) $^+$  381.1888 found, 381.1997.



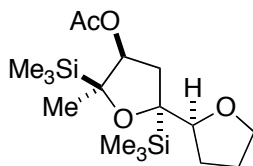
**3-[(2R,3S)-3-((2R,3S)-3-methyl-3-silanyl-oxiran-2-yl)-3-silanyl-oxiran-2-yl]propan-1-ol (2):** To a solution of acetate **23** (1.3 g, 3.7 mmol) in THF (8.0 mL) and MeOH (8.0 mL) at 0 °C was added a 1.0 M solution of LiOH (8.0 mL) and the mixture stirred 20 min. The mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to afford bisepoxide **2** (1.0 g, 84%):  $R_f = 0.47$  (50% EtOAc in hexane);  $[\alpha]_D^{25} = +4.4$  ( $c = 18.3$ ,  $\text{CHCl}_3$ ); IR (thin film, NaCl) 3445, 2957, 2360, 2341, 1441, 1418, 1371, 1250, 1062, 840, 756  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.68 (dt,  $J = 5.5, 4.0$  Hz, 2H), 2.88 (dd,  $J = 7.9, 4.0$  Hz, 1H), 2.71 (dd, 8.2, 3.7 Hz, 1H), 2.16 (dd,  $J = 14.3, 3.4$  Hz, 1H), 1.85-1.71 (m, 4H), 1.55-1.28 (m, 2H), 1.19 (s, 3H), 0.17 (s, 9H), 0.08 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  63.7, 62.7, 62.4, 56.7, 55.1, 38.4, 30.5, 27.6, 22.9, -0.9, -1.5; HR-MS (ESI) Calcd for  $\text{C}_{15}\text{H}_{32}\text{O}_3\text{Si}_2$  ( $\text{M} + \text{H}$ ) $^+$  317.1968 found, 317.1958.



**3**

**(2*S*,4*R*,5*R*,2'*S*)-5-Methyl-2,5-bis-trimethylsilyl-octahydro-[2,2']bifuranyl-4-ol (3):**

To a solution of bisepoxide **2** (10 mg, 32  $\mu$ mol) in  $\text{CH}_2\text{Cl}_2$  (0.3 mL) at  $-78^\circ\text{C}$  was added  $\text{Et}_2\text{O}\cdot\text{BF}_3$  (7 mg, 32  $\mu$ mol) and the mixture stirred 2 h. The reaction was quenched with saturated  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 2$  mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford bisfuran **3** (5.0 mg, 50%): IR (thin film, NaCl) 3375, 2953, 1739, 1451, 1246, 1052, 1063, 839  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.80 (d,  $J = 11.6$  Hz, 1H), 3.99-3.94 (m, 2H), 3.88-3.83 (m, 1H), 3.79-3.74 (m, 1H), 2.26 (dd,  $J = 14.0, 5.8$  Hz, 1H), 1.95-1.91 (m, 3H), 1.82 (d,  $J = 14$  Hz, 1H), 1.33-1.28 (m, 1H), 0.94 (s, 3H), 0.09 (s, 9H), 0.06 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  85.1, 83.3, 82.1, 81.1, 67.0, 35.7, 29.6, 26.1, 25.4,  $-1.5$ ,  $-1.8$ ; HR-MS (ESI) Calcd for  $\text{C}_{15}\text{H}_{33}\text{O}_3\text{Si}_2$  ( $\text{M} + \text{H}$ ) $^+$  317.1963, found 317.1967.

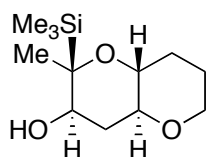


**24**

**Acetic acid (2*S*,4*R*,5*R*,2'*S*)-5-methyl-2,5-bis-trimethylsilyl-octahydro-[2,2']bifuranyl-4-yl ester (24):** To a solution of bisfuran **3** (6 mg, 19  $\mu$ mol) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL) was added *i*- $\text{Pr}_2\text{EtN}$  (80 mg, 0.6 mmol),  $\text{Ac}_2\text{O}$  (60 mg, 0.6 mmol), and DMAP (2 mg, 16  $\mu$ mol). The mixture stirred overnight and was quenched with saturated  $\text{NH}_4\text{Cl}$  and concentrated *in vacuo*. The remaining contents were extracted with  $\text{Et}_2\text{O}$  ( $3 \times 3$  mL). The combined organic layers were washed with water, brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford acetate **24** (5.0 mg, 87%):  $R_f = 0.47$  (20% EtOAc in hexane);  $[\alpha]_D^{25} = -50.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ); IR (thin film, NaCl) 2959, 1743, 1450, 1368,



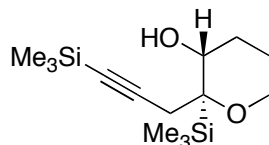
1246, 1109, 1072, 1045, 838, 754  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.16 (d,  $J = 5.6$  Hz, 1H), 3.95-3.91 (m, 1H), 3.88-3.83 (m, 1H), 3.63-3.59 (m, 1H), 2.42 (dd,  $J = 14.6, 5.8$  Hz, 1H), 2.20 (d,  $J = 14.6$  Hz, 1H), 2.02 (s, 3H), 1.96-1.82 (m, 4H), 1.03 (s, 3H), 0.07 (s, 18H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 85.3, 84.8, 82.0, 80.0, 68.0, 39.6, 28.4, 26.0, 25.0, 21.7,  $-0.6$ ,  $-1.8$ ; HR-MS (ESI) Calcd for  $\text{C}_{17}\text{H}_{34}\text{NaO}_4\text{Si}_2$  ( $\text{M} + \text{Na}$ ) $^+$  381.1888, 381.1893.



4

**(2R,3R,4aS,8aR)-2-Methyl-2-trimethylsilanyl-octahydro-pyrano[3,2-b]pyran-3-ol:**

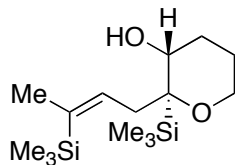
To bisepoxide **2** (20 mg, 0.1 mmol) was added a 1.92 M solution of  $\text{Cs}_2\text{CO}_3$  in MeOH (1.0 mL). The resulting solution was heated to 55-60  $^\circ\text{C}$  for 5 days. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc ( $3 \times 5$  mL). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude material was purified by column chromatography to afford diad **4** (2.1 mg, 14%):  $R_f = 0.48$  (50%, EtOAc in hexane);  $[\alpha]_D^{25} = +20.9$  ( $c = 4.3$ , in  $\text{CHCl}_3$ ); IR (thin film, NaCl) 3444, 2953, 2865, 1453, 1347, 1248, 1100, 1069, 1039, 839  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.93-3.89 (m, 1H), 3.58 (dd,  $J = 11.6, 5.2$  Hz, 1H), 3.41-3.35 (m, 1H), 3.12 (ddd,  $J = 13.1, 8.9, 4.3$  Hz, 1H), 2.98 (ddd,  $J = 13.4, 9.2, 4.6$  Hz, 1H), 2.19 (app dt,  $J = 11.6, 4.9$  Hz, 1H), 2.03-1.97 (m, 1H), 1.80-1.69 (m, 3H), 1.40-1.31 (m, 1H), 1.28 (s, 3H), 0.19 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  77.6, 77.0, 75.5, 74.3, 68.0, 37.3, 29.9, 25.9, 25.2, 0.3; HR-MS (ESI) Calcd for  $\text{C}_{12}\text{H}_{24}\text{NaO}_3\text{Si}$  ( $\text{M} + \text{Na}$ ) $^+$  267.1387, found 267.1385.



**25**

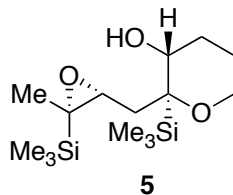
**(2R,3R)-2-Trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (25):** To olefin (Z)-5,8-Bis-trimethylsilanyl-oct-4-en-7-yn-1-ol<sup>4</sup> (6.4 g, 24 mmol) was added CH<sub>3</sub>CN/DMM (760 mL, 1:2 v:v), a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (500 mL), *n*-Bu<sub>4</sub>NHSO<sub>4</sub> (1.6 g, 4.8 mmol), and chiral ketone **A** (12 g, 48 mmol). To this solution was added, simultaneously over 20 min *via* pressure equalizing addition funnels, a solution of Oxone<sup>®</sup> (59 g, 96 mmol) in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (400 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (400 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture stirred 10 min then diluted with water (800 mL) and extracted with hexane (3 × 400 mL). The combined organic layers were dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst by column chromatography and was carried on to the next step as a mixture.

To a solution of the crude epoxide in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) at 0 °C was added Et<sub>2</sub>O·BF<sub>3</sub> (0.3 mL, 1.2 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated NaHCO<sub>3</sub>. The aqueous layer was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was purified by column chromatography (10-20% EtOAc in hexane) to afford alkyne **25** (0.9 g, 19% over two steps): R<sub>f</sub> = 0.53 (20%, EtOAc in hexane); [α]<sub>D</sub><sup>25</sup> = -20.0 (*c* = 2.0, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3470, 2957, 2175, 1249, 1089, 1003, 842, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.96 (m, 1H), 3.68 (ddd, *J* = 12.2, 9.5, 3.4 Hz, 1H), 3.54 (app dt, *J* = 11.9, 4.6 Hz, 1H), 2.88 (d, *J* = 16.8 Hz, 1H), 2.45 (d, *J* = 17.1 Hz, 1H), 2.29 (d, *J* = 4.6 Hz, 1H), 2.02-1.95 (m, 1H), 1.89-1.80 (m, 1H), 1.74-1.68 (m, 1H), 1.52-1.45 (m, 1H), 0.20 (s, 9H), 0.15 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 104.4, 88.9, 75.2, 70.7, 61.6, 28.7, 25.7, 22.1, 0.6, -0.2; HR-MS (ESI) Calcd for C<sub>14</sub>H<sub>28</sub>NaO<sub>2</sub>Si<sub>2</sub> (M + Na)<sup>+</sup> 307.1520, found 307.1517.

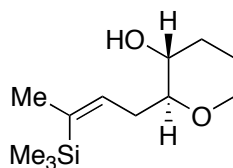


**12**

**(2*R*,3*R*)-2-Trimethylsilanyl-2-((*Z*)-3-trimethylsilanyl-but-2-enyl)-tetrahydro-pyran-3-ol (12):** To a solution of alkyne **25** (100 mg, 0.35 mmol) in Et<sub>2</sub>O (1 ml) at 0 °C was added dropwise DIBALH (neat, 187  $\mu$ l, 1.05 mmol). After gas evolution had ceased the solution was heated to reflux for 18h. The solution was cooled to 0 °C and treated with MeLi (1.6 M in Et<sub>2</sub>O, 0.57 ml, 0.91 mmol). After stirring at room temperature for 1h the solution was cooled to –78 °C. CuCN (32 mg, 0.35 mmol) and LiCl (30 mg, 0.7 mmol) were weighed into a flask in a glove box under Ar. THF (1ml) was added and the solution stirred at room temperature for 5 min before cooling to –78 °C. The solution of CuCN•2LiCl was added by cannula to the vinyl alanate solution at –78 °C before addition of a solution of methyl iodide (88  $\mu$ l, 1.4 mmol) in THF (500 ml). The solution was warmed to room temperature over 2 h then heated to 40 °C for 2 h. The reaction mixture was poured on to 1N HCl (5 ml) and ice. The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (4 x 5 ml). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield olefin **12** (73 mg, 69%):  $R_f$  = 0.64 (20% EtOAc in hexane);  $[\alpha]_D^{25}$  = –17.0 ( $c$  = 1.2, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3486, 2953, 2932, 2869, 1249, 1086, 1069, 1016, 835, 756 cm<sup>–1</sup>; <sup>1</sup>H NMR  $\delta$  (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.09 (app tq,  $J$  = 6.9, 1.9 Hz, 1H), 3.75-3.66 (m, 2H), 3.51 (ddd,  $J$  = 10.7, 6.3, 3.6 Hz, 1H), 2.56-2.51 (m, 2H), 1.99-1.88 (m, 1H), 1.85-1.62 (m, 3H) 1.77 (d,  $J$  = 1.7 Hz, 3H), 1.56-1.44 (m, 1H), 0.15 (s, 9H), 0.14 (s, 9H); <sup>13</sup>C NMR  $\delta$  (125 MHz, CDCl<sub>3</sub>)  $\delta$  137.8, 137.1, 76.4, 71.0, 62.5, 35.7, 28.1, 25.6, 23.3, 0.4, 0.3; HR-MS (ESI) Calcd for C<sub>15</sub>H<sub>32</sub>NaO<sub>2</sub>Si<sub>2</sub> (M + Na)<sup>+</sup> 323.1833, found 323.1831.

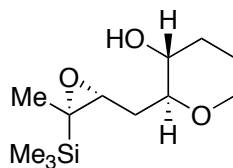


**(2*S*,3*R*)-2-((2*R*,3*S*)-3-Methyl-3-trimethylsilyl-oxiranylmethyl)-2-trimethylsilyl-tetrahydro-pyran-3-ol (5):** To olefin **12** (140 mg, 0.46 mmol) was added CH<sub>3</sub>CN/DMM (16 mL, 1:2 v:v), a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (10.2 mL), *n*-Bu<sub>4</sub>NHSO<sub>4</sub> (0.03 g, 0.09 mmol), and chiral ketone **A** (220 mg, 0.87 mmol). To this solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (0.22 g, 0.87 mmol) in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (7.5 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (7.5 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture stirred 10 min then diluted with water (50 mL) and extracted with hexane (3 × 50 mL). The combined organic layers were dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to yield epoxide **5** (90 mg, 62%, dr >95:5): R<sub>f</sub> = 0.49 (20% EtOAc in hexane); [α]<sub>D</sub><sup>25</sup> = +18.3 (*c* = 6.0, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3436, 2955, 2854, 1440, 1408, 1370, 1250, 1091, 1025, 837, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.06 (app dt, *J* = 9.8, 4.6 Hz, 1H), 3.79-3.74 (m, 1H), 3.55 (app dt, *J* = 10.4, 3.0 Hz, 1H), 3.09 (dd, *J* = 8.5, 1.2 Hz, 1H), 2.10 (d, *J* = 5.5 Hz, 1H), 2.06 (dd, *J* = 15.0, 1.2 Hz, 1H), 1.97-1.93 (m, 1H), 1.78-1.70 (m, 4H), 1.24 (s, 3H), 0.18 (s, 9H), 0.13 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 77.1, 72.0, 64.6, 61.9, 54.2, 36.3, 29.4, 25.6, 23.3, 0.9, – 1.1; HR-MS (ESI) Calcd for C<sub>15</sub>H<sub>32</sub>NaO<sub>3</sub>Si<sub>2</sub> (M + Na)<sup>+</sup> 339.1782, found 339.1772.



**(2*S*,3*R*)-2-((*Z*)-3-Trimethylsilylbut-2-enyl)-tetrahydro-pyran-3-ol (15):** To a solution of olefin **12** (0.20 g, 0.67 mmol) in THF (6.5 mL) was added a 1 M solution of TBAF in THF (2.0 mL). The reaction mixture stirred at room temperature overnight then

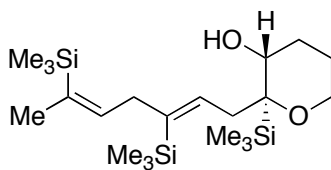
was quenched with water (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to afford monodesilylated olefin **15** (0.14 g, 95%): *R<sub>f</sub>* = 0.27 (20% EtOAc in hexane); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = −23.9 (*c* = 9.2, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3422, 2945, 2853, 1618, 1442, 1248, 1097, 1035, 838, 756 cm<sup>−1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.13 (app tq, *J* = 6.3, 1.7 Hz, 1H), 3.91–3.87 (m, 1H), 3.37 (ddd, *J* = 13.6, 8.8, 4.7 Hz, 1H), 3.31 (dt, *J* = 11.1, 3.5 Hz, 1H), 3.06 (ddd, *J* = 11.7, 7.2, 4.6 Hz, 1H), 2.66–1.60 (m, 1H), 2.34–2.27 (m, 1H), 2.11–2.05 (m, 2H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.70–1.63 (m, 1H), 1.43–1.34 (m, 1H), 0.15 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  138.8, 138.0, 83.0, 78.0, 71.6, 68.4, 35.8, 33.4, 26.2, 25.6, 0.5; HR-MS (ESI) Calcd for C<sub>12</sub>H<sub>24</sub>NaO<sub>2</sub>Si (M + Na)<sup>+</sup> 251.1438, found 251.1433.



**11**

**(2*S*,3*R*)-2-((2*R*,3*S*)-3-Methyl-3-trimethylsilyl-oxiranylmethyl)-tetrahydro-pyran-3-ol (**11**):** To olefin **15** (96 mg, 0.42 mmol) was added CH<sub>3</sub>CN/DMM (12.8 mL, 1:2 v:v), a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>−4</sup> M Na<sub>2</sub>-(EDTA) (8 mL), *n*-Bu<sub>4</sub>NHSO<sub>4</sub> (26 mg, 0.8 mmol), and chiral ketone **A** (0.192 g, 0.74 mmol). To this solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (930 g, 1.51 mmol) in 4.0 × 10<sup>−4</sup> M Na<sub>2</sub>-(EDTA) (6.4 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (6.4 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture stirred 20 min then diluted with water (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic layers were dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude material was purified by column chromatography (10–20% EtOAc in hexane) to yield epoxide **11** (87 mg, 85%, dr >95:5): *R<sub>f</sub>* = 0.46 (20% EtOAc in hexane); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +8.6 (*c* = 4.7, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3438, 2956, 2853, 1440, 1251, 1097, 1039, 841, 756 cm<sup>−1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.92 (m, 1H), 3.64 (ddd,

$J = 15.4, 9.2, 4.4$  Hz, 1H), 3.36 (app dt,  $J = 11.3, 3.7$  Hz, 1H), 3.22 (ddd,  $J = 8.9, 5.3, 2.9$  Hz, 1H), 3.01 (dd,  $J = 9.5, 2.4$  Hz, 1H), 2.37 (d,  $J = 4.7$  Hz, 1H), 2.16-2.09 (m, 2H), 1.77-1.66 (m, 2H), 1.47-1.38 (m, 1H), 1.24 (s, 3H), 0.13 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  81.9, 70.1, 68.8, 62.7, 55.3, 33.8, 32.7, 26.6, 23.3, -1.1; HR-MS (ESI) Calcd for  $\text{C}_{12}\text{H}_{24}\text{NaO}_3\text{Si}$  ( $\text{M} + \text{Na}$ ) $^+$  267.1387, found 267.1385.



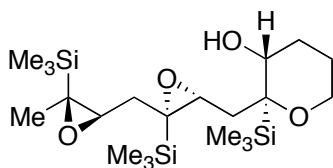
**13**

**(2R,3R)-2-((2Z,5Z)-3,6-bistrimethylsilanylhepta-2,5-dienyl)-2-trimethylsilanyl-tetrahydropyran-3-ol (13):** To a stirred solution of (Z)-3-trimethylsilyl-2-buten-1-ol<sup>5</sup> (500 mg, 3.47 mmol) in  $\text{Et}_2\text{O}$  (12 mL) at 0 °C under argon was added  $\text{PBr}_3$  (166  $\mu\text{L}$ , 1.74 mmol) and stirred for 2 h. The reaction was quenched by addition of a saturated solution of  $\text{NaHCO}_3$  (2 mL). The aqueous layer was separated and extracted with  $\text{Et}_2\text{O}$  (3 x 5 mL). The combined organic layers were washed with water (3 x 5 mL), brine, dried over  $\text{MgSO}_4$ , filtered through a pad of silica and concentrated *in vacuo*. The crude bromide was used without further purification. Using a modified procedure based on the work of Lipshutz,<sup>6</sup> a solution of alkyne **25** (50 mg, 0.18 mmol) in THF (350  $\mu\text{L}$ ) was added to  $\text{Cp}_2\text{ZrHCl}$  (136 mg, 0.53 mmol) under Ar. The resulting slurry was heated at 50°C for 3 h then cooled to -78°C and treated with MeLi (1.6 M in  $\text{Et}_2\text{O}$ , 120  $\mu\text{L}$ , 0.19 mmol). The mixture was allowed to warm to room temperature over 1 h and then recooled to -78 °C. A solution of  $\text{Me}_2\text{CuCNLi}_2$  was added dropwise (prepared by addition of MeLi (1.6M in  $\text{Et}_2\text{O}$ , 240  $\mu\text{L}$ , 0.89 mmol) to a slurry of CuCN (17 mg, 0.19 mmol) in  $\text{Et}_2\text{O}$  (200  $\mu\text{L}$ ) at 0°C under Ar and stirring for 10 min). After 15 min a solution of the crude (Z)-4-bromobut-2-en-2-yl-trimethylsilane (146 mg, 0.70 mmol) in THF (700  $\mu\text{L}$ ) was added. The reaction was heated at 50°C for 15 h. The reaction was quenched by addition of aqueous  $\text{NH}_4\text{OH}/\text{NH}_4\text{Cl}$  (10% v/v) in saturated (2 mL). The

<sup>5</sup> Han, S.; Kass, S. R. *Tetrahedron Lett.* **1997**, 38, 7503.

<sup>6</sup> Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, 112, 7440.

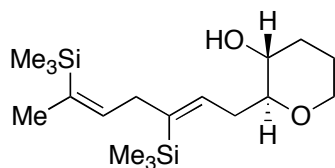
product was extracted with Et<sub>2</sub>O (4 x 20 mL) and dried over MgSO<sub>4</sub>. The solution was filtered through a pad of celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield the diene **13** (23 mg, 32%, >95% *Z*): R<sub>f</sub> = 0.38 (10% EtOAc in hexane); [α]<sub>D</sub><sup>25</sup> = -3.76 (c = 2.6, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3447, 2952, 2854, 2360, 2341, 1247, 1091, 836, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.07 (tt, *J* = 6.4, 1.6 Hz, 1H), 5.91 (tq, *J* = 7.2, 1.8 Hz, 1H), 3.75-3.66 (m, 2H), 3.52 (ddd, *J* = 11.4, 5.9, 3.9 Hz, 1H), 2.88-2.84 (m, 2H), 2.70 (ddt, *J* = 16.3, 6.4, 1.6 Hz, 1H), 2.51 (ddt, *J* = 16.0, 6.6, 1.6 Hz, 1H), 1.97-1.87 (m, 2H), 1.75-1.85 (m, 1H), 1.77 (q, *J* = 1.4 Hz, 3H), 1.64-1.72 (m, 1H), 1.44-1.52 (m, 1H), 0.17 (s, 9H), 0.14 (s, 9H), 0.11 (s, 9H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) 141.5, 140.2, 137.7, 135.7, 75.9, 70.3, 61.6, 39.2, 35.3, 27.1, 24.9, 22.4, 0.3, 0.1, -0.3; HR-MS (ESI) Calcd for C<sub>21</sub>H<sub>44</sub>NaO<sub>2</sub>Si<sub>3</sub> (M+Na)<sup>+</sup> 435.2541, found 435.2545.



**7**

**(2*R*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilyl-oxiranylmethyl)-3-trimethylsilyl-oxiranylmethyl]-2-trimethylsilyl-tetrahydro-pyran-3-ol (7):** To a solution of the diene **13** (40 mg, 97 μmol) was added CH<sub>3</sub>CN/DMM (3.1 mL, 1:2 v:v), a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (2.1 mL), *n*-BuNH<sub>2</sub>SO<sub>4</sub> (7 mg, 21 μmol), and chiral ketone **A** (50 mg, 0.2 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (0.20 g, 0.33 mmol) in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (1.4 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (1.4 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture was diluted with water and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (350 μL) and to this was added NaHCO<sub>3</sub> (29 mg, 350 μmol), and *m*-CPBA

(12 mg, 68  $\mu$ mol) and the reaction stirred 15 min. The reaction was quenched with 1 M NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  5 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to afford bisepoxide **7** (18 mg, 38%, dr 89:11):  $R_f$  = 0.55 (30% EtOAc in hexane);  $[\alpha]_D^{25}$  = +17.4 ( $c$  = 2.3, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3442, 2955, 2853, 2360, 1250, 1091, 838, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.08-4.02 (m, 1H); 3.66 (dt,  $J$  = 11.4, 3.5 Hz, 1H), 3.42 (td,  $J$  = 11.4, 2.8 Hz, 1H), 3.17 (dd,  $J$  = 8.7, 1.3 Hz, 1H), 2.66 (d,  $J$  = 7.1 Hz, 1H), 2.65 (d,  $J$  = 7.1 Hz, 1H), 2.18-2.06 (m, 2H), 1.98-1.90 (m, 2H), 1.79-1.69 (m, 2H), 1.68-1.60 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), 0.00 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  76.8, 72.0, 64.4, 62.8, 60.6, 55.5, 38.5, 36.5, 29.6, 25.6, 23.3, 0.9, -0.4, -1.1; HR-MS (ESI) Calcd for C<sub>21</sub>H<sub>44</sub>NaO<sub>4</sub>Si<sub>3</sub> (M + Na)<sup>+</sup> 467.2445, found 467.2443.



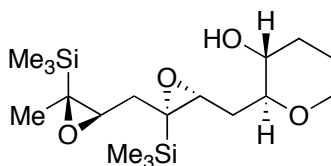
**16**

**(2R,3R)-2-((2Z,5Z)-3,6-bis(trimethylsilyl)hepta-2,5-dienyl)-tetrahydropyran-3-ol**

**(16):** To a solution of diene **13** (86 mg, 0.2 mmol) in THF (2.1 mL) was added a 1 M solution of TBAF in THF (2.1 mL). The reaction mixture was stirred at 40 °C for 4 h. The reaction was quenched with water and extracted with Et<sub>2</sub>O (4  $\times$  20 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to afford monodesilylated diene **16** (60 mg, 85%):  $R_f$  = 0.30 (20% EtOAc in hexane);  $[\alpha]_D^{25}$  = -6.6 ( $c$  = 9.1, in CHCl<sub>3</sub>); IR (thin film, NaCl) 3405, 2951, 2852, 2360, 1616, 1442, 1248, 1097, 836 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.12 (ddt,  $J$  = 8.0, 6.2, 1.5 Hz, 1H), 5.90 (tq,  $J$  = 7.0, 1.6 Hz, 1H), 3.90 (ddt,  $J$  = 11.4, 3.9, 1.7 Hz, 1H), 3.29-3.43 (m, 2H), 3.09 (ddd,  $J$  = 8.8, 7.0, 4.9 Hz, 1H), 2.87-2.89 (m, 2H), 2.67 (ddd,  $J$  = 14.6, 8.2, 4.9 Hz, 1H), 2.32-2.39 (m, 1H), 2.06-2.13 (m, 1H), 1.78 (dd,  $J$  = 2.8, 1.4 Hz, 3H), 1.65-1.72 (m, 2H), 1.36-1.46 (m, 1H), 0.18 (s, 9H), 0.12 (s, 9H); <sup>13</sup>C NMR

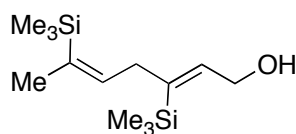


(100 MHz, CDCl<sub>3</sub>)  $\delta$  141.3, 141.0, 138.8, 135.7, 82.5, 71.3, 67.8, 39.6, 35.7, 32.8, 25.7, 24.9, 0.4, 0.0; HR-MS (ESI) Calcd for C<sub>18</sub>H<sub>36</sub>NaO<sub>2</sub>Si<sub>2</sub> (M + Na)<sup>+</sup> 363.2146, found 363.2151.



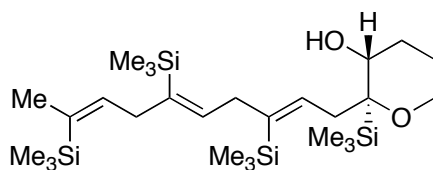
**18**

**(2*S*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (18):** To a solution of the diene **16** (0.1 g, 0.4 mmol) in CH<sub>3</sub>CN/DMM (12.0 mL, 1:2 v:v) was added a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (8.0 mL), *n*-Bu<sub>4</sub>NHSO<sub>4</sub> (30 mg, 80 μmol), and chiral ketone **A** (0.2 g, 0.8 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (0.8 g, 1.3 mmol) in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (5.3 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (5.3 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, 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) to yield bisepoxide **18** (27 mg, 29%, dr 92:8): R<sub>f</sub> = 0.53 (50% EtOAc in hexane); [α]<sub>D</sub><sup>25</sup> = -2.62 (*c* = 26.7, CHCl<sub>3</sub>); IR (thin film, NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 840, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.93-3.88 (m, 1H), 3.60-3.54 (m, 1H), 3.34 (td, *J* = 11.3, 4.0 Hz, 1H), 3.22 (ddd, *J* = 9.0, 5.6, 3.2 Hz, 1H), 3.16 (dd, *J* = 8.7, 3.1 Hz, 1H), 2.74 (dd, *J* = 7.5, 4.3 Hz, 1H), 2.33 (br s, 1H-OH), 2.16 (dt, *J* = 14.8, 3.2 Hz, 1H), 2.11-2.07 (m, 1H), 2.01 (dd, *J* = 14.6, 4.1 Hz, 1H), 1.76 (ddd, *J* = 14.8, 8.9, 6.0 Hz, 1H), 1.73-1.63 (m, 2H), 1.56 (dd, *J* = 14.8, 7.5 Hz, 1H), 1.48-1.37 (m, 1H), 1.19 (s, 3H), 0.18 (s, 9H), 0.09 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  81.7, 70.3, 68.6, 62.7, 61.1, 56.5, 55.6, 38.4, 34.0, 33.0, 26.5, 23.3, -0.5, -1.1; HR-MS (ESI) Calcd for C<sub>18</sub>H<sub>36</sub>NaO<sub>4</sub>Si<sub>2</sub> (M + Na)<sup>+</sup> 395.2044, found 395.2040.



**26**

**(2Z,5Z)-3,6-Bis-trimethylsilyl-hepta-2,5-dien-1-ol (26):** To a slurry of CuCN (1.28 g, 14.29 mmol) in Et<sub>2</sub>O (36 mL) at 0 °C was added a 1.6 M solution of MeLi in Et<sub>2</sub>O (17.9 mL). After 15 min a solution of (2Z,5E)-6-Iodo-3,6-bis-trimethylsilyl-hexa-2,5-dien-1-ol<sup>7</sup> (3.15 g, 6.35 mmol) in Et<sub>2</sub>O (5.0 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<sub>4</sub>Cl. The aqueous layer was separated and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield the dienol **26** (1.69 g, 4.4 mmol, 69%): R<sub>f</sub> = 0.45 (10% EtOAc in hexane); IR (thin film, NaCl) 3315, 2954, 2898, 1616, 1444, 1406, 1249, 1035, 996, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.12 (t, *J* = 7.0 Hz, 1H), 5.96-5.89 (m, 1H), 4.21 (t, *J* = 5.5 Hz, 2H), 3.48-3.55 (m, 1H), 2.84 (d, *J* = 7.0 Hz, 2H), 1.79 (s, 3H), 1.47-1.44 (m, 1H), 0.17 (s, 9H), 0.12 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 143.8, 141.0, 140.9, 137.0, 62.9, 39.4, 25.4, 0.9, 0.5; HR-MS (ESI) Calcd for C<sub>13</sub>H<sub>28</sub>NaOSi<sub>2</sub> (M + Na)<sup>+</sup> 279.1576, found 279.1576.



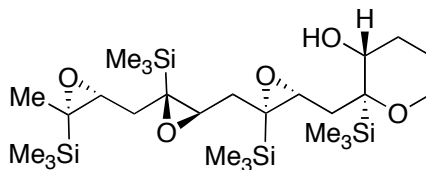
**14**

**(2R,3R)-2-(Trimethyl-silanyl)-2-((2Z,5Z,8Z)-3,6,9-tris-trimethylsilyl-deca-2,5,8-trienyl)-tetrahydropyran-3-ol (14):** To a stirred solution of dienol **26** (890 mg, 2.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.6 ml) maintained at 0 °C under argon was added NEt<sub>3</sub> (647 μl, 4.6 mmol) and methanesulfonyl chloride (198 μl, 2.55 mmol) and stirred for 15 min. The reaction mixture was diluted with water (5 ml) and citric acid was added until pH 3-4.

<sup>7</sup> Heffron, T. P.; Trenkle, J. D.; Jamison, T. F. *Tetrahedron* **2003**, 59, 8913-8917.

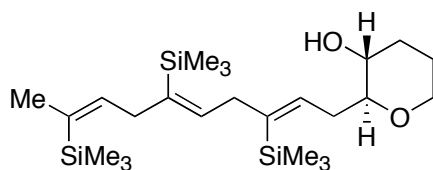
The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 5 ml). The combined organic layers were washed with water (3 x 5 ml), brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude dienyl mesylate product **27** was used without further purification. Using a modified procedure based on the work of Ziegler:<sup>8</sup> To a stirred solution of **25** (570 mg, 2.0 mmol) in Et<sub>2</sub>O (4 ml) maintained at 0 °C under argon, was added DIBALH (neat, 1.07 ml, 6.0 mmol). After gas evolution had ceased the solution was heated to reflux for 20 h. The solution was cooled to 0 °C and treated with MeLi (1.6M in Et<sub>2</sub>O, 1.4 ml, 2.24 mmol). The mixture was allowed to warm to room temperature over 1.5 h and then recooled to –78 °C. To the reaction mixture was added a solution of CuI•P(OEt)<sub>3</sub> (713 mg, 2.0 mmol) in THF (7.0 ml). To the resulting light brown mixture was added a cooled solution of crude dienyl mesylate **27** in THF (1.0 ml) at –78 °C. The reaction mixture was allowed to warm slowly to room temperature over 18 h. The reaction mixture was poured on to 1N HCl (50 ml) and ice. The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (4 x 50 ml). The combined organic layers were washed with saturated aqueous NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to give the desired triene **14** (321 mg, 31%, >95% *Z*): R<sub>f</sub> = 0.39 (20% EtOAc in hexane); [α]<sub>D</sub><sup>25</sup> = –6.0 (c = 1.67 in CHCl<sub>3</sub>); IR (thin film, NaCl) 3461, 2953, 2897, 1613, 1444, 1247, 1092, 836, 756 cm<sup>–1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.08 (t, *J* = 6.4 Hz, 1H), 5.96–5.87 (m, 2H), 3.75–3.65 (m, 2H), 3.48–3.55 (m, 1H), 2.89 (d, *J* = 7.0 Hz, 2H), 2.86 (d, *J* = 7.0 Hz, 2H), 2.65 (AB dd, *J* = 15.8, 5.8 Hz, 1H) and 2.54 (AB dd, *J* = 16.2, 6.7 Hz, 1H), 2.01–1.98 (m, 1H), 1.85 (d, *J* = 7.6, 1H), 1.87–1.77 (m, 1H), 1.78 (s, 3H), 1.76–1.65 (m, 1H), 1.54–1.46 (m, 1H), 0.21 (s, 9H), 0.18 (s, 9H), 0.17 (s, 9H), 0.15 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 142.0, 141.8, 140.1, 138.8, 137.8, 135.2, 75.8, 70.4, 61.8, 39.8, 39.2, 35.3, 27.3, 24.8, 22.6, 0.4, 0.3, 0.1, –0.2 ; HR-MS (ESI) Calcd for C<sub>27</sub>H<sub>56</sub>NaO<sub>2</sub>Si<sub>4</sub> (M + Na)<sup>+</sup> 547.3250, found 547.3267.

<sup>8</sup> Ziegler, F. E.; Mikami, K. *Tetrahedron Lett.* **1984**, 25, 131.



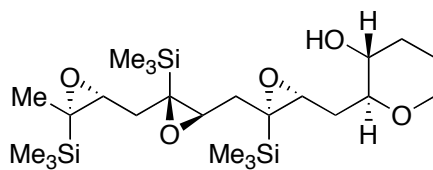
9

**(2*R*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilyl-oxiranylmethyl)-3-trimethylsilyl-oxiranylmethyl)-3-trimethylsilyl-oxiranylmethyl]-2-trimethylsilyl-tetrahydro-pyran-3-ol (9):** To a solution of the triene **14** (89 mg, 0.17 mmol) was added CH<sub>3</sub>CN/DMM (5.3 mL, 1:2 v:v), a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (3.5 mL), *n*-BuNH<sub>2</sub>SO<sub>4</sub> (17.5 mg, 52 μmol), and chiral ketone **A** (130 mg, 0.5 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (626 mg, 1.02 mmol) in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (4.5 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (4.5 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 15 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and to this was added NaHCO<sub>3</sub> (180 mg, 2.15 mmol), and *m*-CPBA (148 mg, 0.86 mmol) and the reaction stirred 30 min. The reaction was quenched with 1 M NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 5 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude material was purified by column chromatography (5-20% EtOAc in hexane) to afford trisepoxide epoxide **9** (29 mg, 30%, dr 92:8): R<sub>f</sub> = 0.52 (30% EtOAc in hexane); [α]<sub>D</sub><sup>25</sup> = +24.5 (c = 3.67 in CHCl<sub>3</sub>); IR (thin film, NaCl) 3444 (br), 2955, 2899, 2853, 2360, 1250, 1091, 839, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.02-4.08 (m, 1H), 3.67 (dt, *J* = 11.6, 4.0 Hz, 1H), 3.42 (td, *J* = 11.1, 2.7 Hz, 1H), 3.21 (d, *J* = 8.2, 1.2 Hz, 1H), 2.92 (dd, *J* = 8.5, 3.0 Hz, 1H), 2.71 (dd, *J* = 7.9, 3.7 Hz, 1H), 2.06-2.22 (m, 3H), 1.90-1.98 (m, 1H), 1.68-1.80 (m, 3H), 1.58-1.68 (m, 1H), 1.35-1.47 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), -0.02 (s, 9H), -0.09 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 76.4, 71.4, 63.6, 62.2, 60.3, 60.0, 55.9, 55.0, 54.9, 38.6, 38.4, 36.0, 28.9, 24.8, 22.9, 0.4, -0.9, -0.9, -1.5; HR-MS (ESI) Calcd for C<sub>27</sub>H<sub>56</sub>NaO<sub>5</sub>Si<sub>4</sub> (M + Na)<sup>+</sup> 595.3097, found 595.3107.



**(2S,3R)-2-((2Z,5Z,8Z)-3,6,9-tris-trimethylsilanyl-deca-2,5,8-trienyl)**

**tetrahydropyran-3-ol (17):** To a solution of triene **14** (150 mg, 0.33 mmol) in THF (3.3 mL) was added a 1 M solution of TBAF in THF (1.0 mL). The reaction mixture was stirred at 30 °C overnight. The reaction was quenched with water and extracted with Et<sub>2</sub>O (4 x 20 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (10% EtOAc in hexane) to afford monodesilylated product **17** (83 mg, 56%): *R*<sub>f</sub> = 0.30 (20% EtOAc in hexane);  $[\alpha]_D^{25} = -12.7$  (*c* = 2.36 in CHCl<sub>3</sub>); IR (thin film, NaCl) 3405 (br), 2952, 2896, 2852, 1614, 1441, 1406, 1247, 1098, 836, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.10 (t, *J* = 6.5 Hz, 1H), 5.87-5.95 (m, 2H), 3.90 (br d, *J* = 10.5 Hz, 1H), 3.33-3.42 (m, 1H), 3.34-3.27 (m, 1H), 3.03-3.10 (m, 1H), 2.92 (d, *J* = 7.0 Hz, 2H), 2.86 (d, *J* = 7.0 Hz, 2H), 2.72-2.64 (m, 1H), 2.39-2.30 (m, 1H), 2.12-2.05 (m, 1H), 1.78 (s, 3H), 1.72-1.63 (m, 3H), 1.45-1.33 (m, 1H), 0.17 (s, 9H), 0.13 (s, 9H), 0.12 (s, 9H) □; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 141.8, 141.7, 140.7, 139.0, 138.8, 135.2, 82.5, 71.0, 67.8, 39.9, 39.1, 35.4, 32.9, 25.7, 24.8, 0.4, 0.3, 0.1 ; HRMS calculated for C<sub>24</sub>H<sub>48</sub>NaO<sub>2</sub>Si<sub>3</sub> 475.2854, found 475.2861.

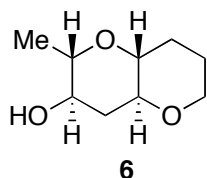


**19**

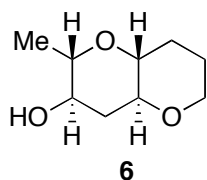
**(2S,3R)-2-[(2R,3S)-3-((2R,3S)-3-((2R,3S)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (19):** To a solution of the triene **17** (77 mg, 0.17 mmol) was added CH<sub>3</sub>CN/DMM (5.3 mL, 1:2 v:v), a 0.05 M solution of Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10 H<sub>2</sub>O in 4.0 × 10<sup>-4</sup> M Na<sub>2</sub>-(EDTA) (3.5 mL), *n*-BuNH<sub>2</sub>SO<sub>4</sub> (17.5 mg, 52 μmol), and chiral

ketone **A** (132 mg, 0.5 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone<sup>®</sup> (626 mg, 1.02 mmol) in  $4.0 \times 10^{-4}$  M Na<sub>2</sub>-(EDTA) (4.5 mL) and a 0.89 M solution of K<sub>2</sub>CO<sub>3</sub> (4.5 mL). After the Oxone<sup>®</sup> and K<sub>2</sub>CO<sub>3</sub> solutions had been added, the resulting mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 20 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.1 mL) and to this was added NaHCO<sub>3</sub> (47 mg, 0.56 μmol), and *m*-CPBA (20 mg, 0.11 mmol) and the reaction stirred 30 min. The reaction was quenched with 1 M NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 5 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude material was purified by column chromatography (10-20% EtOAc in hexane) to afford trisepoxide **19** (43 mg, 50%, dr 90:10): R<sub>f</sub> = 0.52 (50% EtOAc in hexane);  $[\alpha]_D^{25} = +2.72$  (c = 3.67 in CHCl<sub>3</sub>); IR (thin film, NaCl) 3455, 2956, 2852, 1440, 1412, 1251, 1096, 840, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.88-3.97 (m, 1H), 3.53-3.63 (m, 1H), 3.32-3.41 (m, 1H), 3.22-3.30 (m, 2H), 2.92 (dd, *J* = 8.0, 4.5 Hz, 1H), 2.71 (dd, *J* = 8.7, 4.0 Hz, 1H), 2.15-2.24 (m, 2H), 2.08-2.15 (m, 1H), 1.85-1.74 (m, 3H), 1.53 (dd, *J* = 14.5, 7.8 Hz, 1H), 1.37-1.48 (m, 1H), 1.25-1.34 (m, 2H), 1.23 (s, 3H), 0.11 (s, 9H), 0.08 (s, 9H), -0.01 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 81.3, 70.1, 68.1, 62.2, 60.4, 60.1, 56.0, 55.8, 55.3, 38.6, 37.6, 38.8, 32.7, 26.0, 22.8, -0.9, -1.1, -1.6; HR-MS (ESI) Calcd for C<sub>24</sub>H<sub>48</sub>NaO<sub>5</sub>Si<sub>3</sub> (M + Na)<sup>+</sup> 523.2702, found 523.2696.

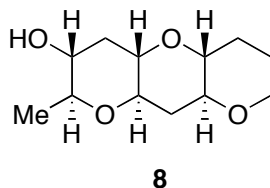
**General Procedure for Base-Promoted Cyclization of Epoxides 5, 7, 9, 11, 18 and 19 (Scheme 2 and Scheme 4):** Cs<sub>2</sub>CO<sub>3</sub> and CsF were weighed into a flame-dried Schlenk tube in a glove box under Ar. To the tube was added a solution of the epoxide in MeOH. The tube was sealed and the resulting slurry heated to 65 °C for 3-5 days. The MeOH was removed *in vacuo* and the reaction mixture partitioned between saturated NH<sub>4</sub>Cl (10 ml) and EtOAc (10 ml). The layers were separated and the aqueous layer extracted with EtOAc (4 x 10ml). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexane) to give the pure product.



**(2*S*,3*R*,4*aS*,8*aR*)-2-methyl-octahydropyrano[3,2-*b*]pyran-3-ol (6):** Following the general procedure, epoxide **5** (4 mg, 12.1  $\mu$ mol) was heated at 65°C with Cs<sub>2</sub>CO<sub>3</sub> (103 mg, 0.32 mmol) and CsF (48 mg, 0.32 mmol) in MeOH (165  $\mu$ l) for 3 days. After standard workup, purification by column chromatography (50-75% EtOAc in hexane) afforded the diad **6** (1.2 mg, 55%);  $R_f$  = 0.34 (60 % EtOAc in hexane);  $[\alpha]_D^{25} = -11.2$  ( $c$  = 0.26 in CHCl<sub>3</sub>); IR (thin film, NaCl) 3413, 2926, 2852, 1114, 1096, 1051, 1026 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.94-3.87 (m, 1H), 3.43-3.32 (m, 2H), 3.23 (ddd,  $J$  = 9.0, 6.1, 6.0 Hz, 1H), 3.06-2.96 (m, 2H), 2.34 (dt,  $J$  = 11.6, 4.3 Hz, 1H), 2.10-2.02 (m, 1H), 1.77-1.68 (m, 2H), 1.52-1.36 (m, 2H), 1.30 (d,  $J$  = 6.1, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  78.5, 77.8, 77.1, 71.8, 68.0, 39.2, 29.5, 25.7, 18.1; HR-MS (ESI) Calcd for C<sub>9</sub>H<sub>16</sub>NaO<sub>3</sub> (M+Na)<sup>+</sup> 195.0992, found 195.0993.

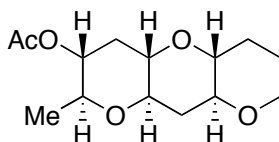


**(2*S*,3*R*,4*aS*,8*aR*)-2-Methyl-octahydropyrano[3,2-*b*]pyran-3-ol (6):** Following the general procedure, epoxide **11** (8 mg, 32.7  $\mu$ mol) was heated at 65°C with Cs<sub>2</sub>CO<sub>3</sub> (267 mg, 0.82 mmol) and CsF (125 mg, 0.82 mmol) in MeOH (427  $\mu$ l) for 3 days to afford the diad **6** (3.5 mg, 62%).



**(2*S*,3*R*,4*aS*,8*aS*,9*aR*,10*aR*)-2-Methyl-decahydro-1,8,10-trioxa-anthracen-3-ol (8):** Following the general procedure, bisepoxide **7** (8 mg, 18  $\mu$ mol) was heated at 65°C with

Cs<sub>2</sub>CO<sub>3</sub> (147 mg, 0.45 mmol) and CsF (68 mg, 0.45 mmol) in MeOH (234  $\mu$ l) for 5 days. After standard workup, purification by column chromatography (50-75% EtOAc in hexane) afforded the triad **8** (1.6 mg, 39%). Spectral data were identical to the previously prepared material.<sup>2</sup>

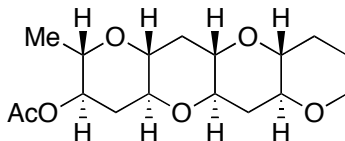


**20**

**(2a*S*,3a*R*,4a*S*,8a*S*,9a*R*,10a*R*)-2-Methyl-decahydro-1,8,10-trioxa-anthracen-3-yl**

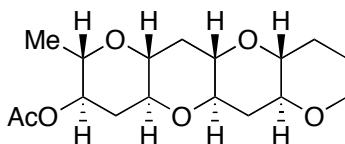
**acetate (20):** Following the general procedure, bisepoxide **18** (17 mg, 46  $\mu$ mol) was heated at 65 °C with Cs<sub>2</sub>CO<sub>3</sub> (300 mg, 0.91 mmol) and CsF (140 mg, 0.91 mmol) in MeOH (480  $\mu$ l) for 3 days. After standard workup, partial purification by column chromatography (50-75% EtOAc in hexane) afforded the crude triad that was taken up in CH<sub>2</sub>Cl<sub>2</sub> (810  $\mu$ L). DMAP (14 mg, 0.11 mmol), pyridine (16  $\mu$ L, 0.11 mmol) and acetic anhydride (11  $\mu$ L, 0.11 mmol) were added and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl. The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 5 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford **20** (4.3 mg, 35% over 2 steps) *R*<sub>f</sub> = 0.60 (50% EtOAc in hexane); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -4.3 (*c* = 0.46, CHCl<sub>3</sub>); IR (thin film, NaCl) 2960, 2866, 2361, 1734, 1653, 1559, 1384, 1259, 1093, 1022, 841, 800 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.56 (ddd, *J* = 11.4, 9.6, 4.8 Hz, 1H), 3.96-3.90 (m, 1H), 3.47-3.35 (m, 2H), 3.19-3.01 (m, 4H), 2.47-2.42 (m, 1H), 2.36-2.30 (m, 1H), 2.12-2.06 (m, 2H), 2.07 (s, 3H), 1.78-1.71 (m, 2H), 1.53-1.42 (m, 2H), 1.20 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.2, 78.4, 76.4, 75.9, 72.4, 68.2, 35.8, 35.3, 29.4, 25.7, 21.3, 18.0; HR-MS (ESI) Calcd for C<sub>14</sub>H<sub>22</sub>NaO<sub>5</sub> (M+Na)<sup>+</sup> 293.1365, found 293.1362.





**10**

**(2R,3S,4aR,5aS,6aR,10aS,11aR,12aS)-2-Methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yl acetate (10):** Following the general procedure, trisepoxide **9** (25 mg, 43  $\mu$ mol) was heated at 65 °C with Cs<sub>2</sub>CO<sub>3</sub> (235 mg, 0.72 mmol) and CsF (109 mg, 0.72 mmol) in MeOH (460  $\mu$ l) for 5 days. After standard workup, partial purification by column chromatography (50-75% EtOAc in hexane) afforded the crude tetrad that was taken up in CH<sub>2</sub>Cl<sub>2</sub> (800  $\mu$ L). DMAP (12 mg, 0.1  $\mu$ mol), pyridine (15  $\mu$ L, 0.1  $\mu$ mol) and acetic anhydride (10  $\mu$ L, 0.1  $\mu$ mol) were added and the mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl. The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 5 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford the acetylated tetrad **10** (2.1 mg, 15%); R<sub>f</sub> = 0.55 (EtOAc); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -7.6 (c = 0.13 in CHCl<sub>3</sub>); IR (thin film, NaCl) 2927, 2861, 1384, 1250, 1097, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  4.52 (ddd, *J* = 11.4, 9.6, 4.8 Hz, 1H), 3.91-3.85 (m, 1H), 3.47-3.32 (m, 2H), 3.18-3.08 (m, 4H), 3.08-2.97 (m, 2H), 2.40 (dt, *J* = 11.1, 4.2 Hz, 1H), 2.32-2.22 (m, 2H), 2.06-2.00 (m, 1H), 2.05 (s, 3H), 1.76-1.67 (m, 2H), 1.52-1.37 (m, 4H), 1.17 (d, *J* = 6.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  170.0, 78.9, 77.7, 77.6, 77.4, 77.1, 76.8, 76.7, 76.2, 72.6, 68.4, 36.1, 35.7, 35.5, 29.8, 26.1, 21.4, 18.1; HR-MS (ESI) Calcd for C<sub>17</sub>H<sub>26</sub>NaO<sub>6</sub> (M+Na)<sup>+</sup> 349.1622, found 349.1616 .

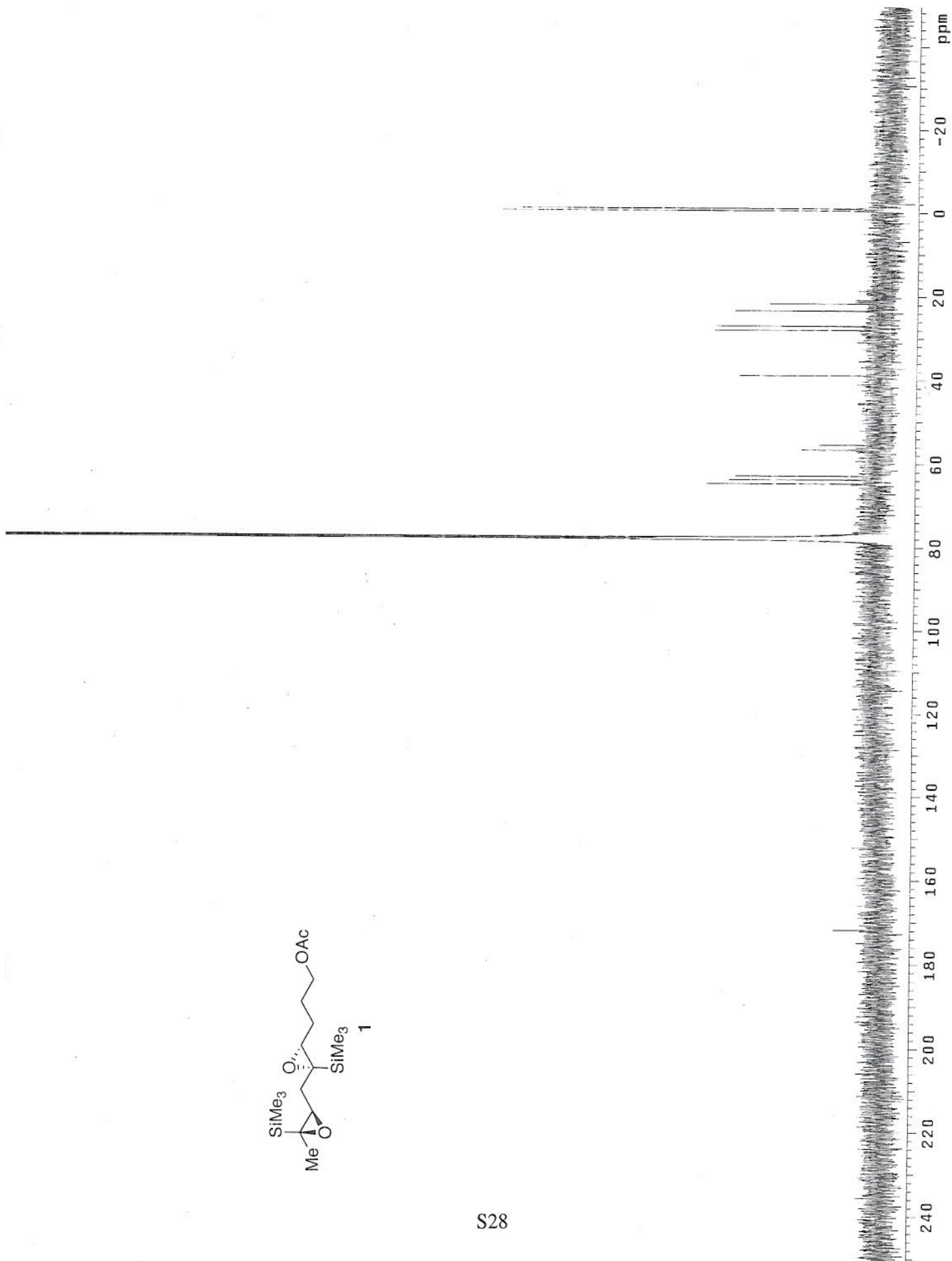


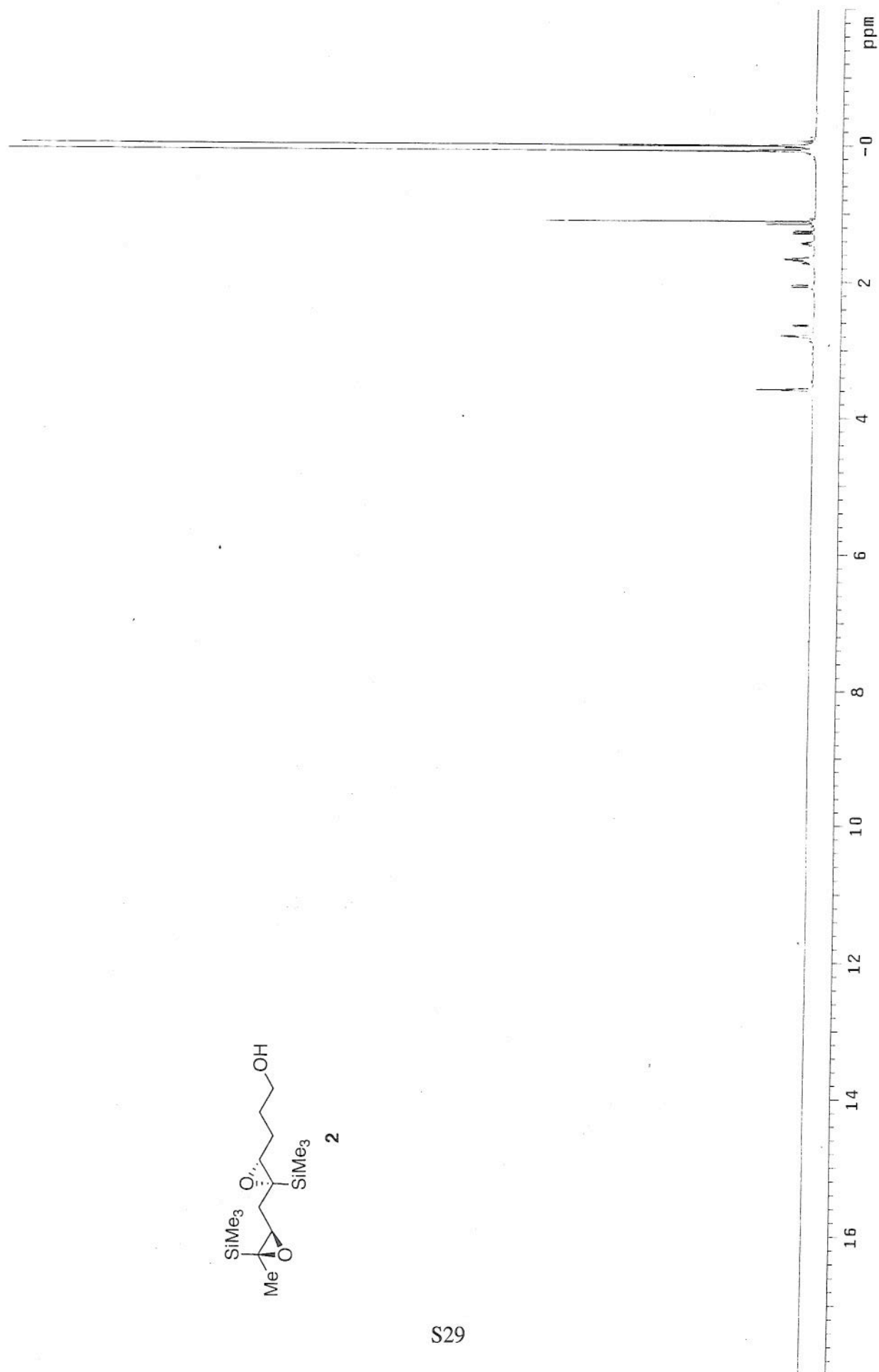
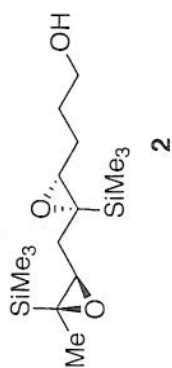
**10**

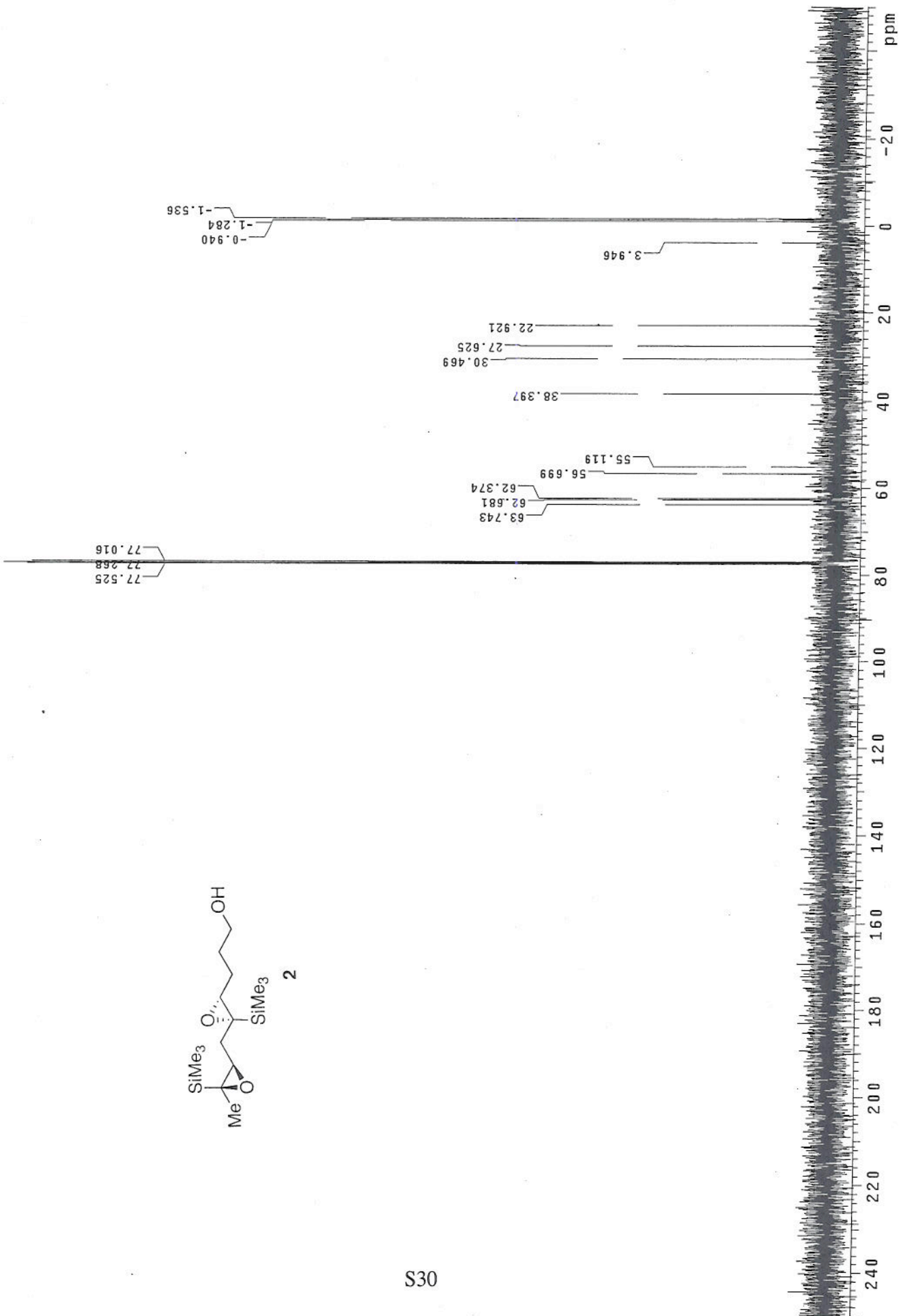
**(2R,3S,4aR,5aS,6aR,10aS,11aR,12aS)-2-Methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yl acetate (10):** Following the general procedure, trisepoxide **19** (18 mg,

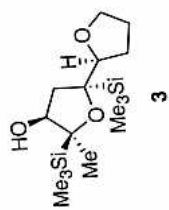
35.9  $\mu\text{mol}$ ) was heated at 65°C with  $\text{Cs}_2\text{CO}_3$  (300 mg, 0.92 mmol) and CsF (140 mg, 0.92 mmol) in MeOH (480  $\mu\text{l}$ ) for 5 days. After standard workup, partial purification by column chromatography (50-75% EtOAc in hexane) afforded the crude tetrad that was taken up in  $\text{CH}_2\text{Cl}_2$  (800  $\mu\text{L}$ ). DMAP (14 mg, 0.1  $\mu\text{mol}$ ), pyridine (16  $\mu\text{L}$ , 0.1 mmol) and acetic anhydride (10  $\mu\text{L}$ , 0.1  $\mu\text{mol}$ ) were added and the mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 5 mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford the acetylated tetrad **10** (2.1 mg, 15%).



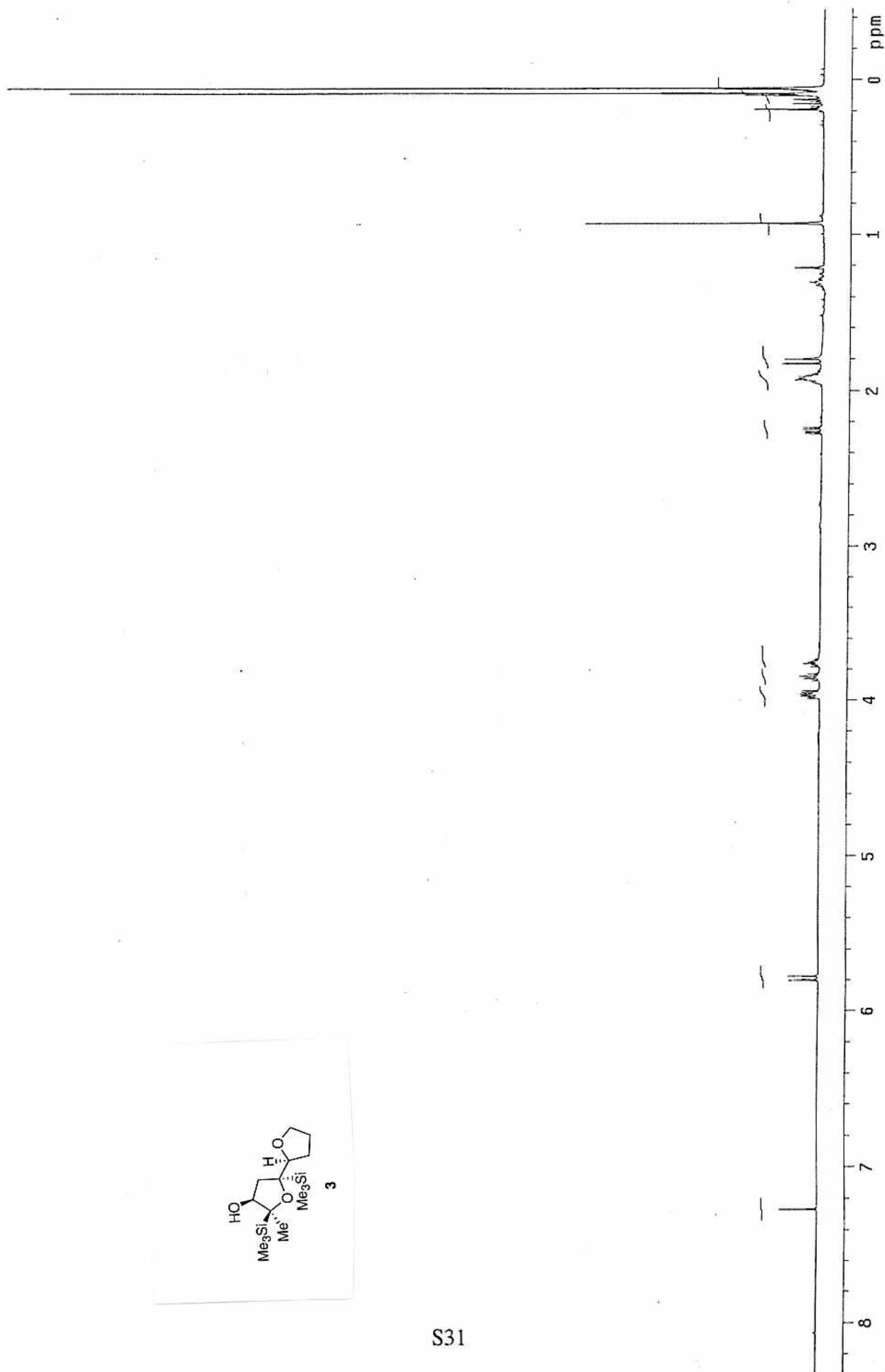


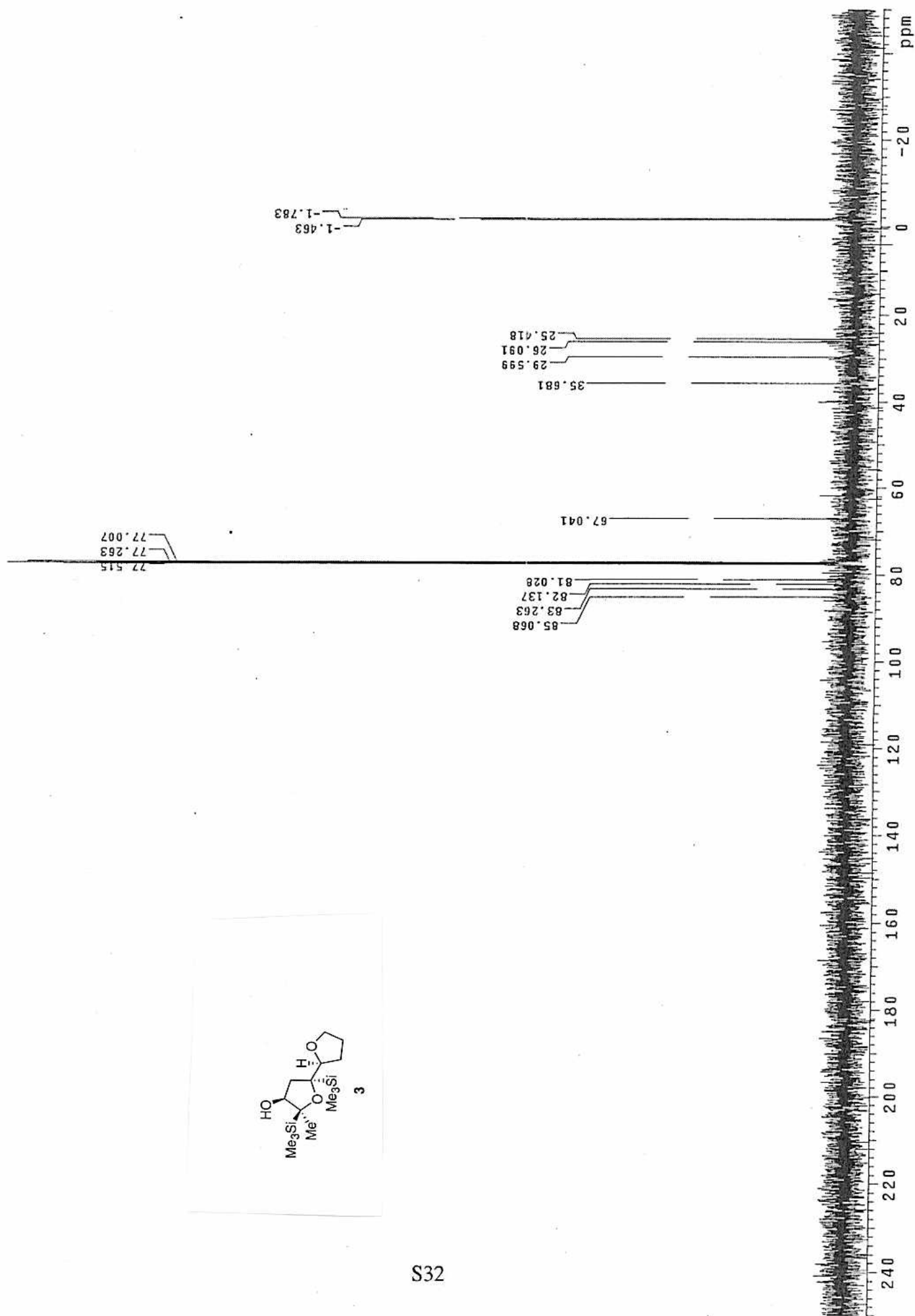




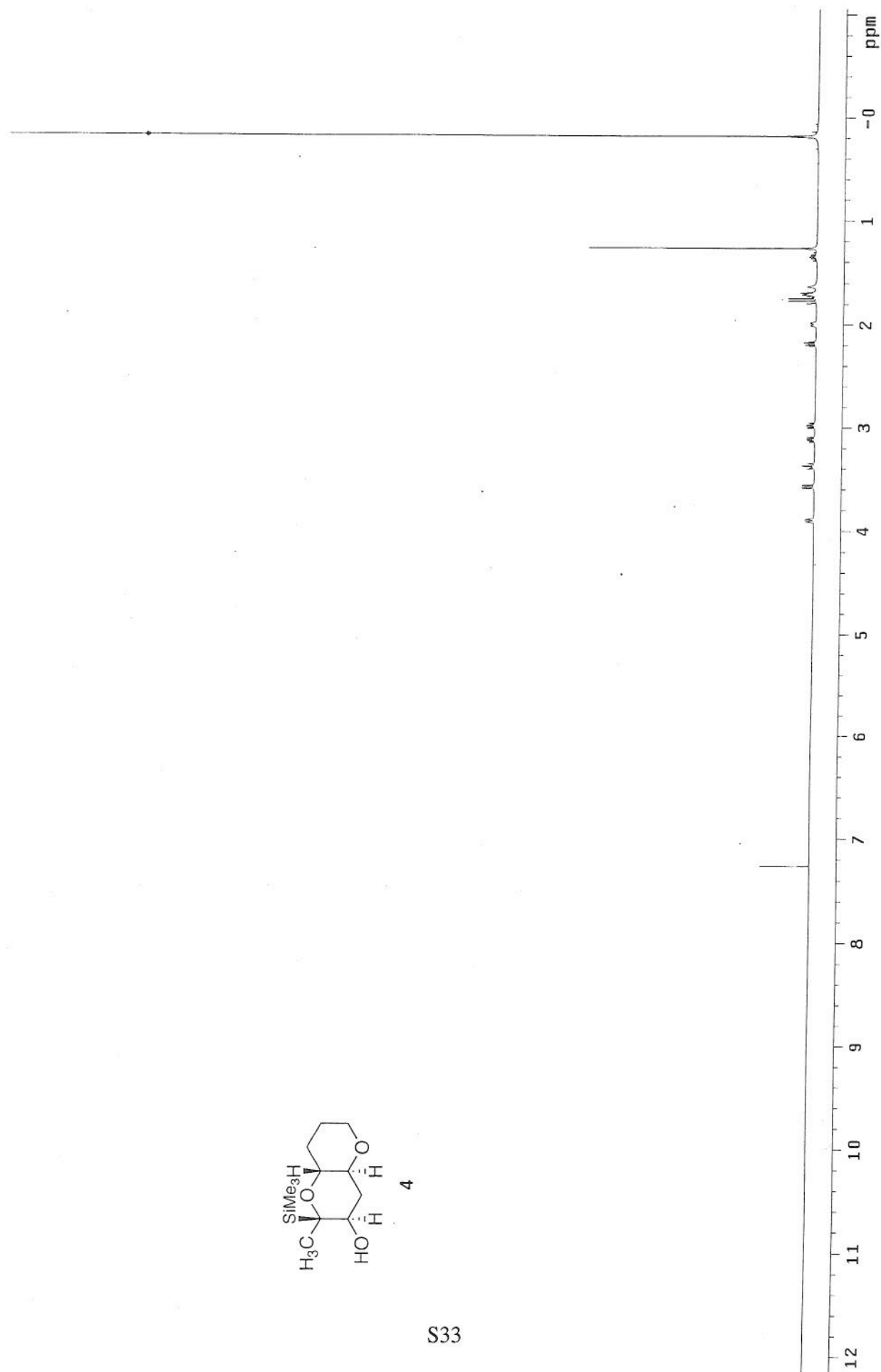
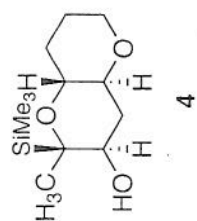


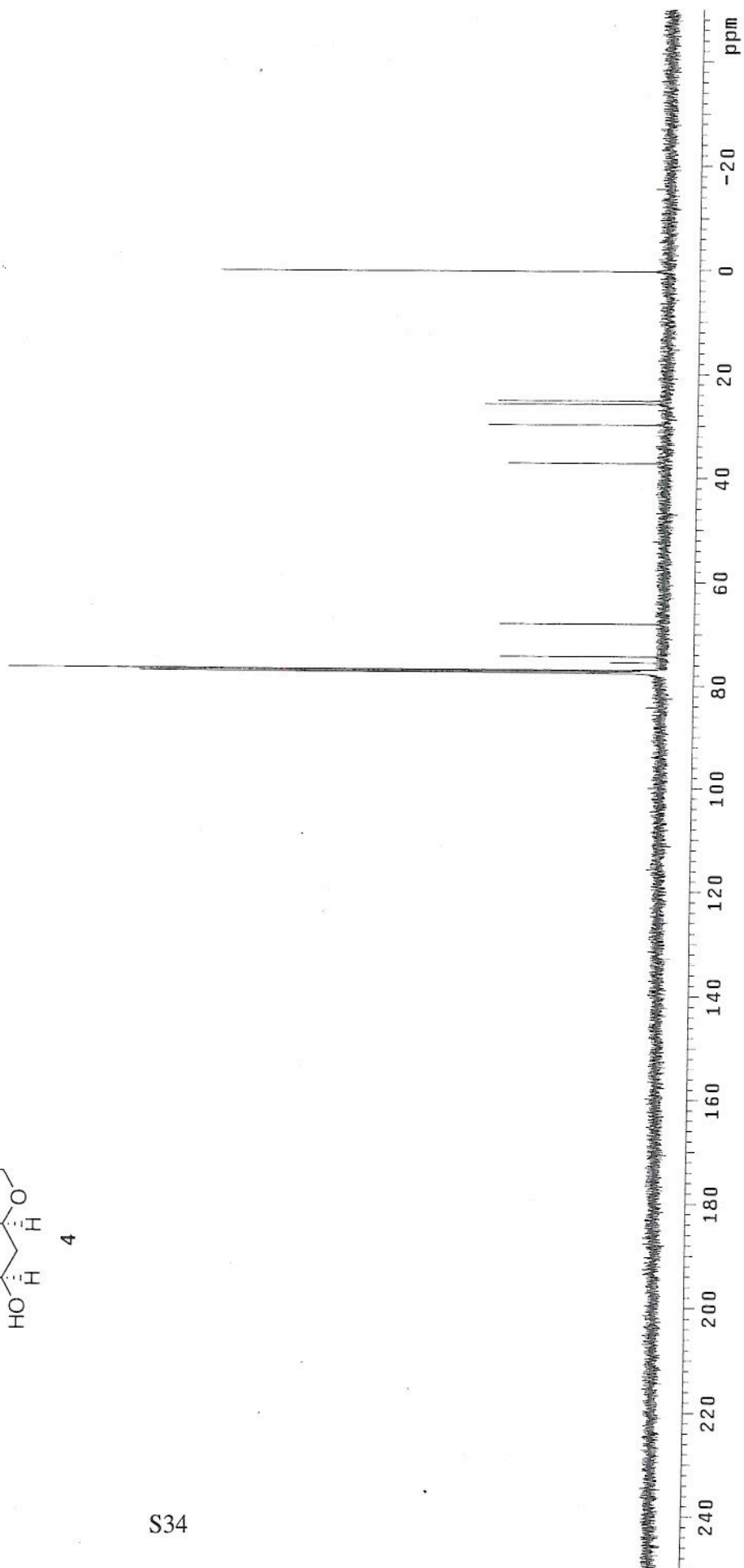
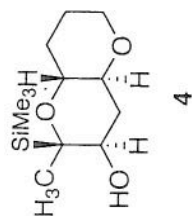
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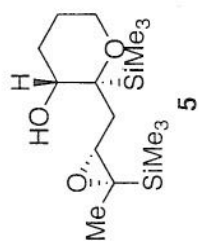




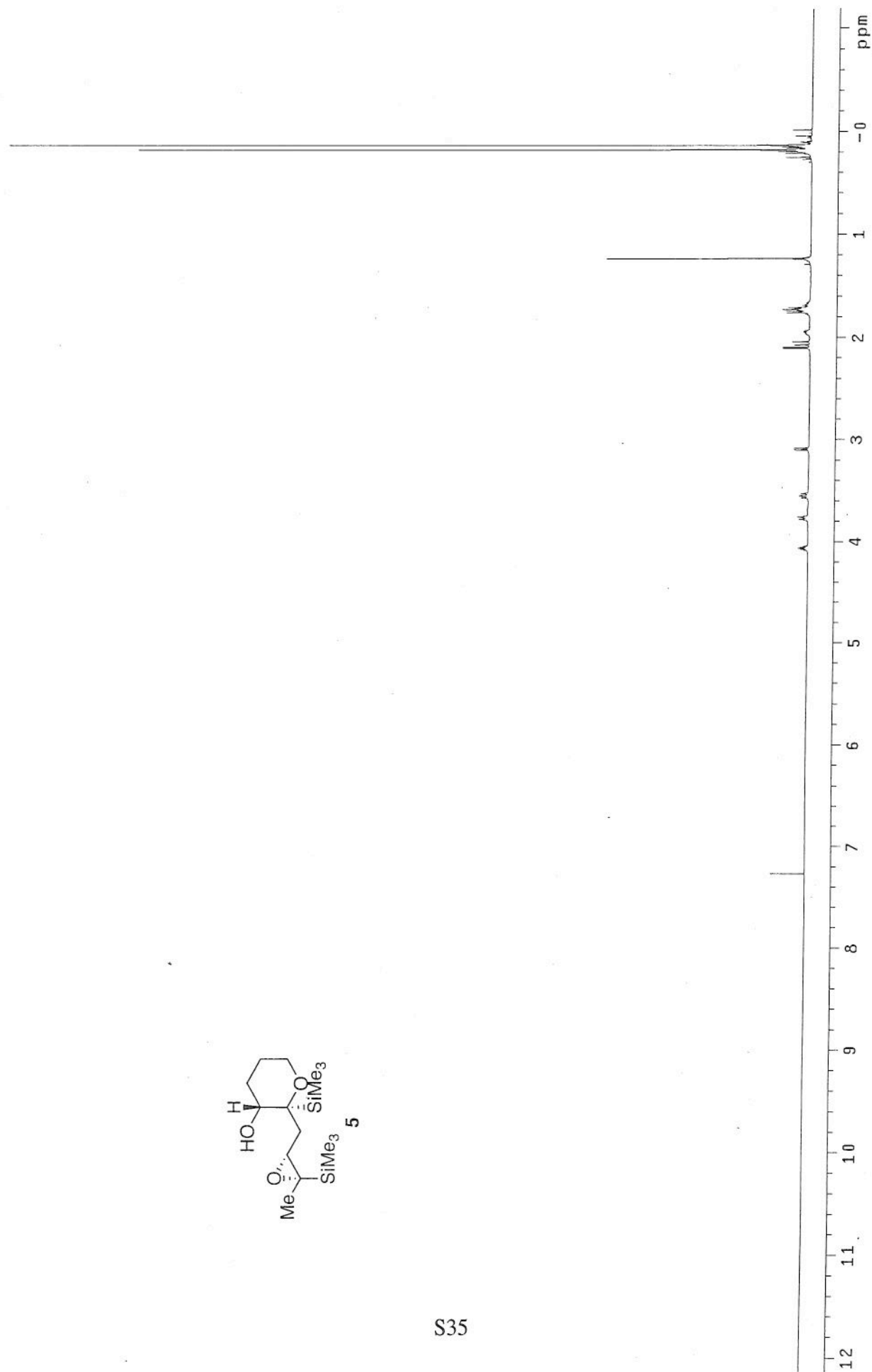


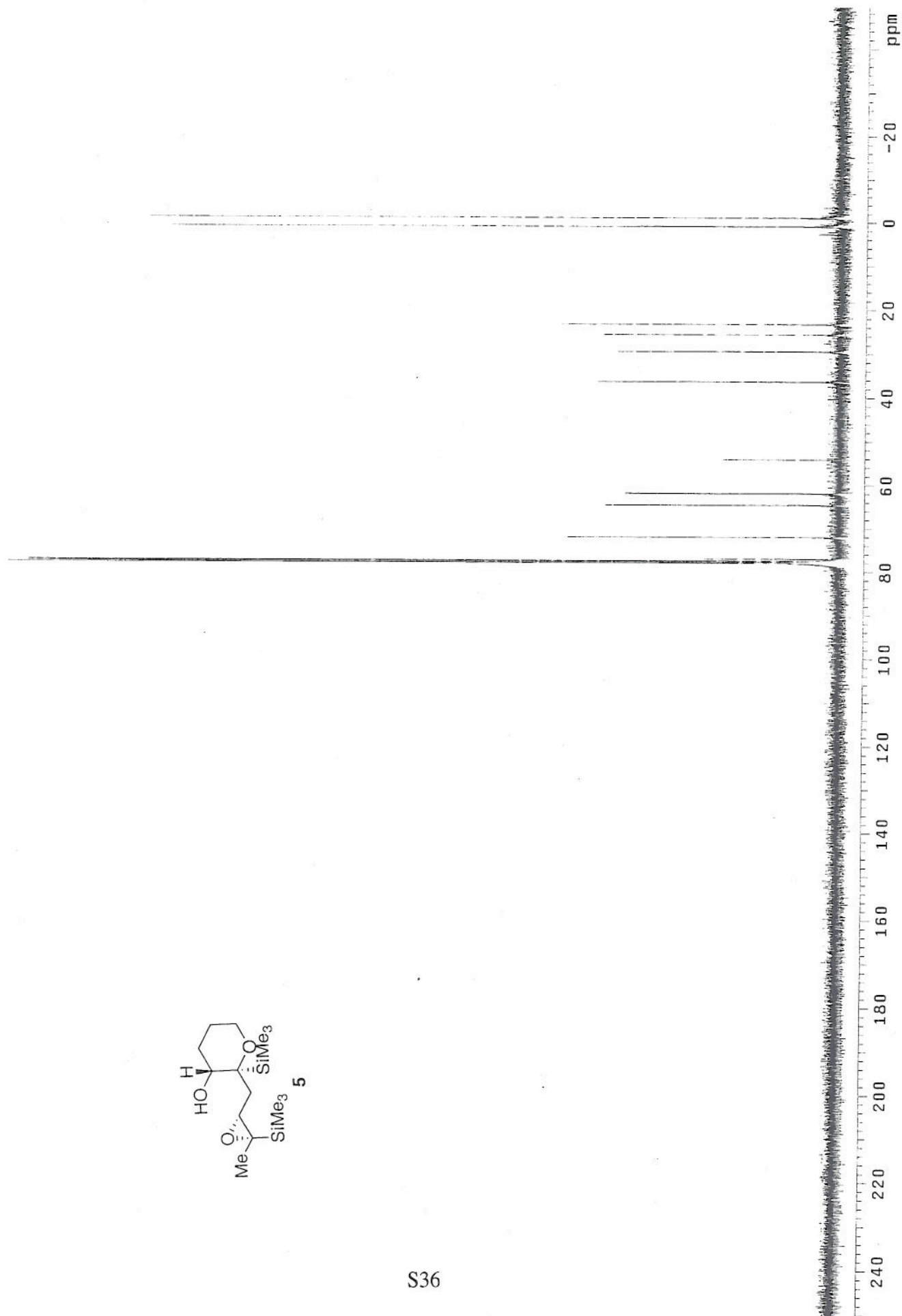
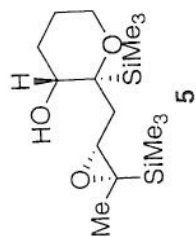


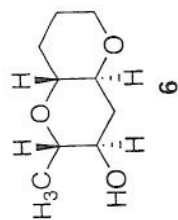




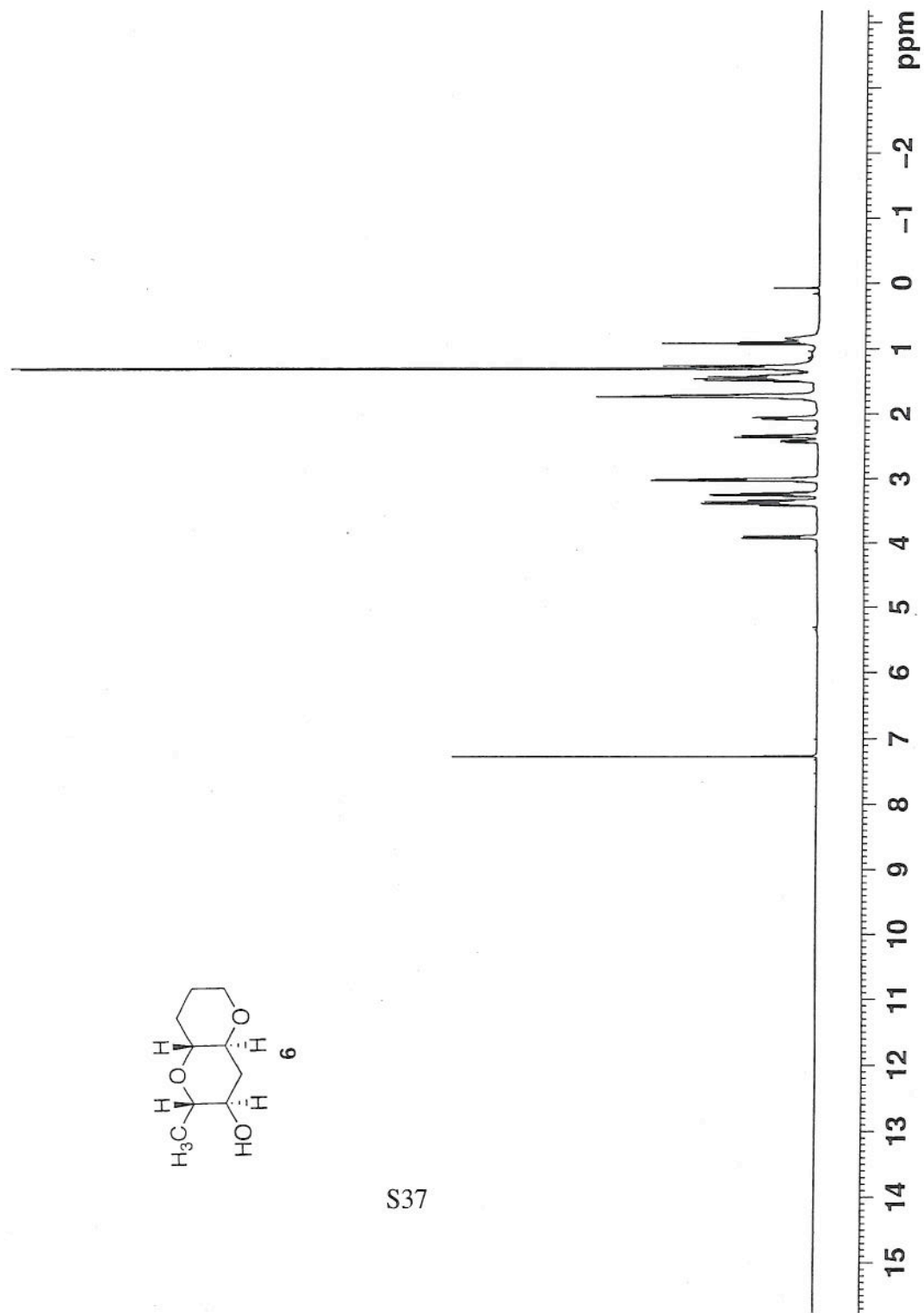
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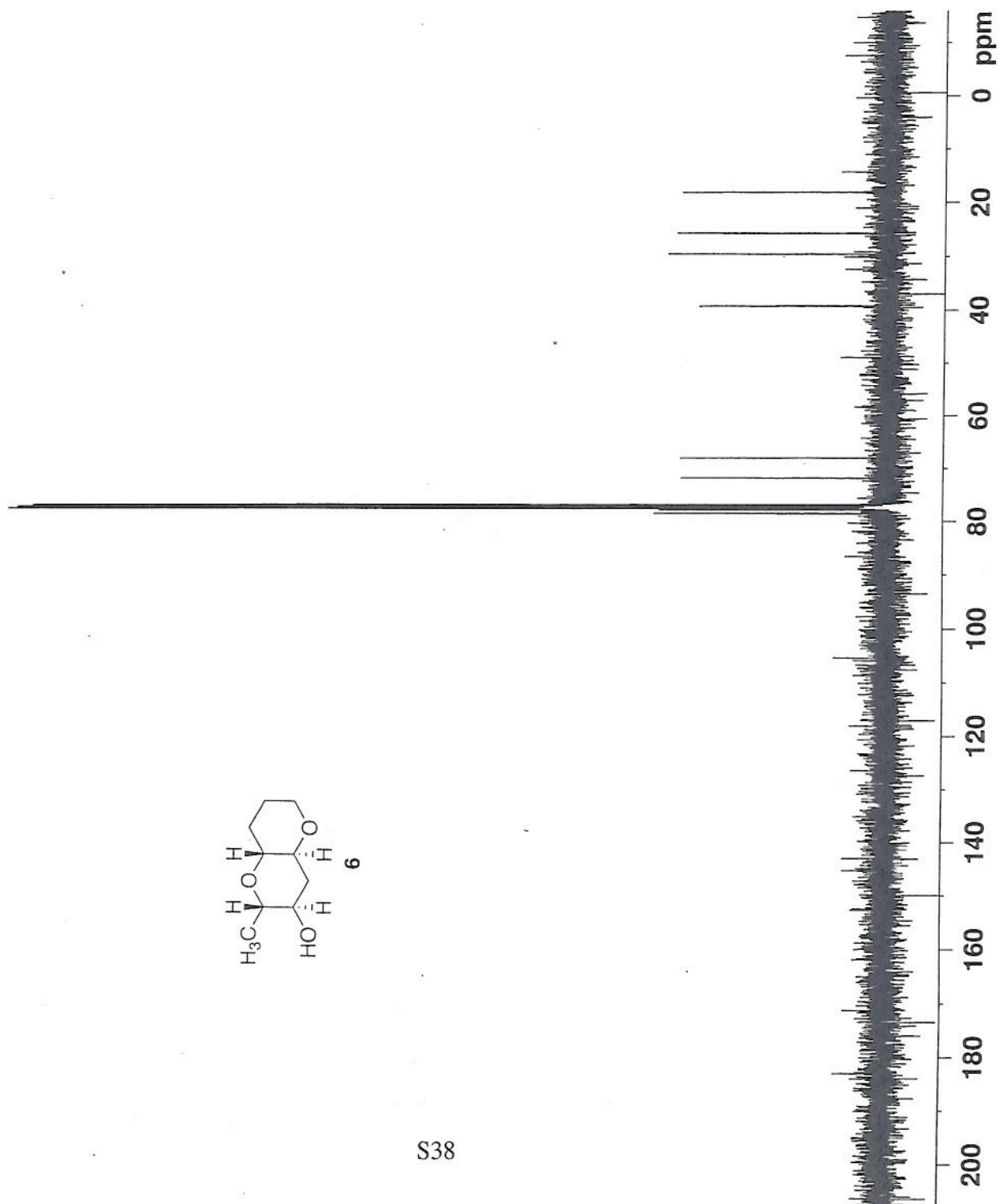
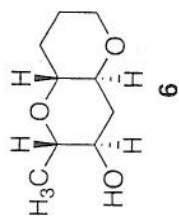


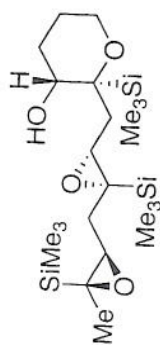




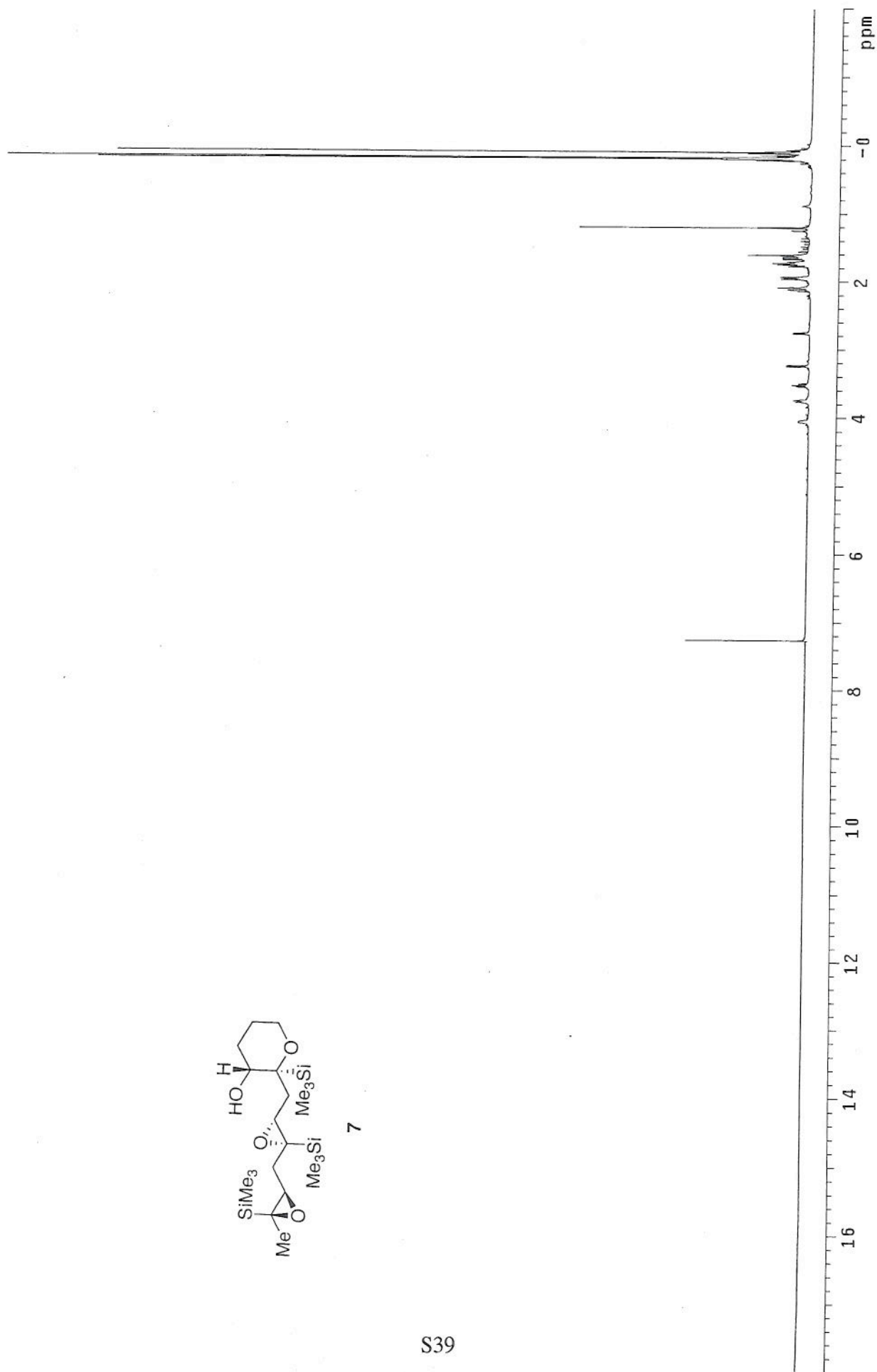
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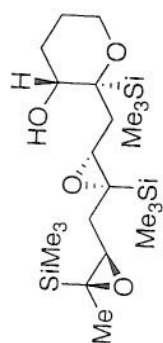






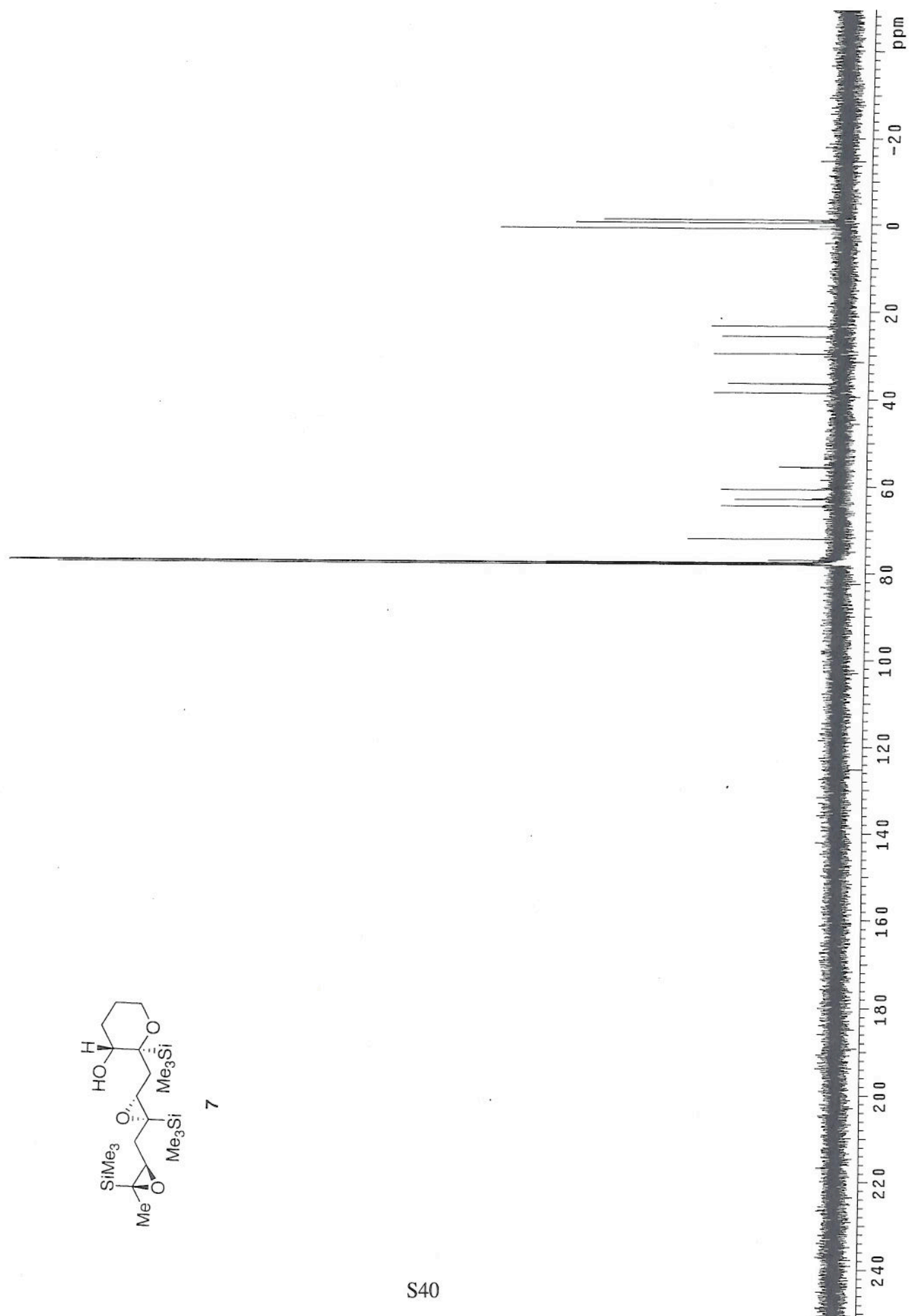
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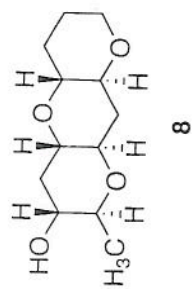


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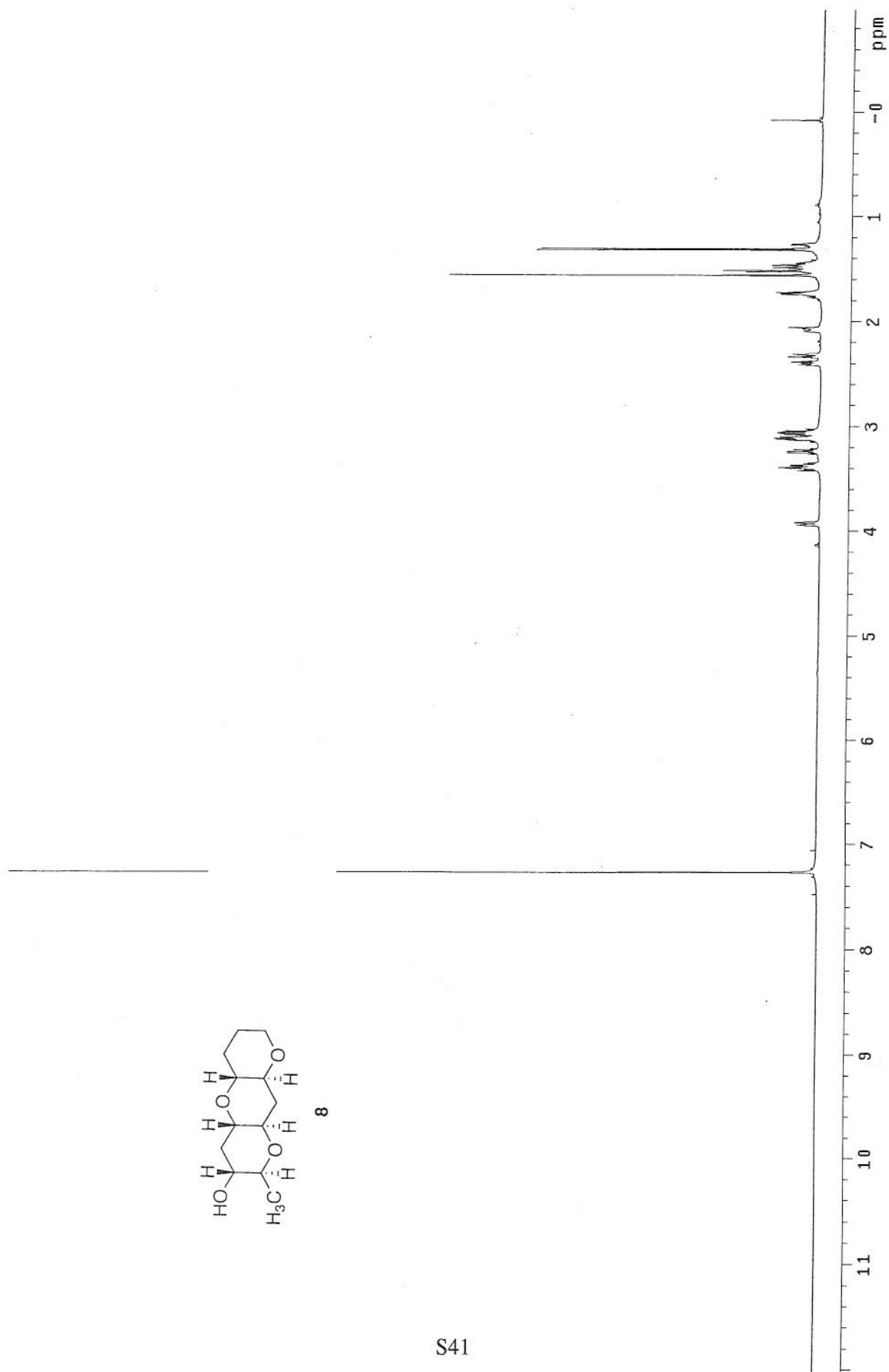
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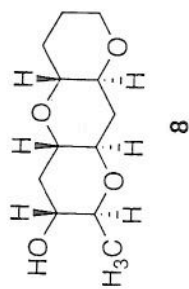




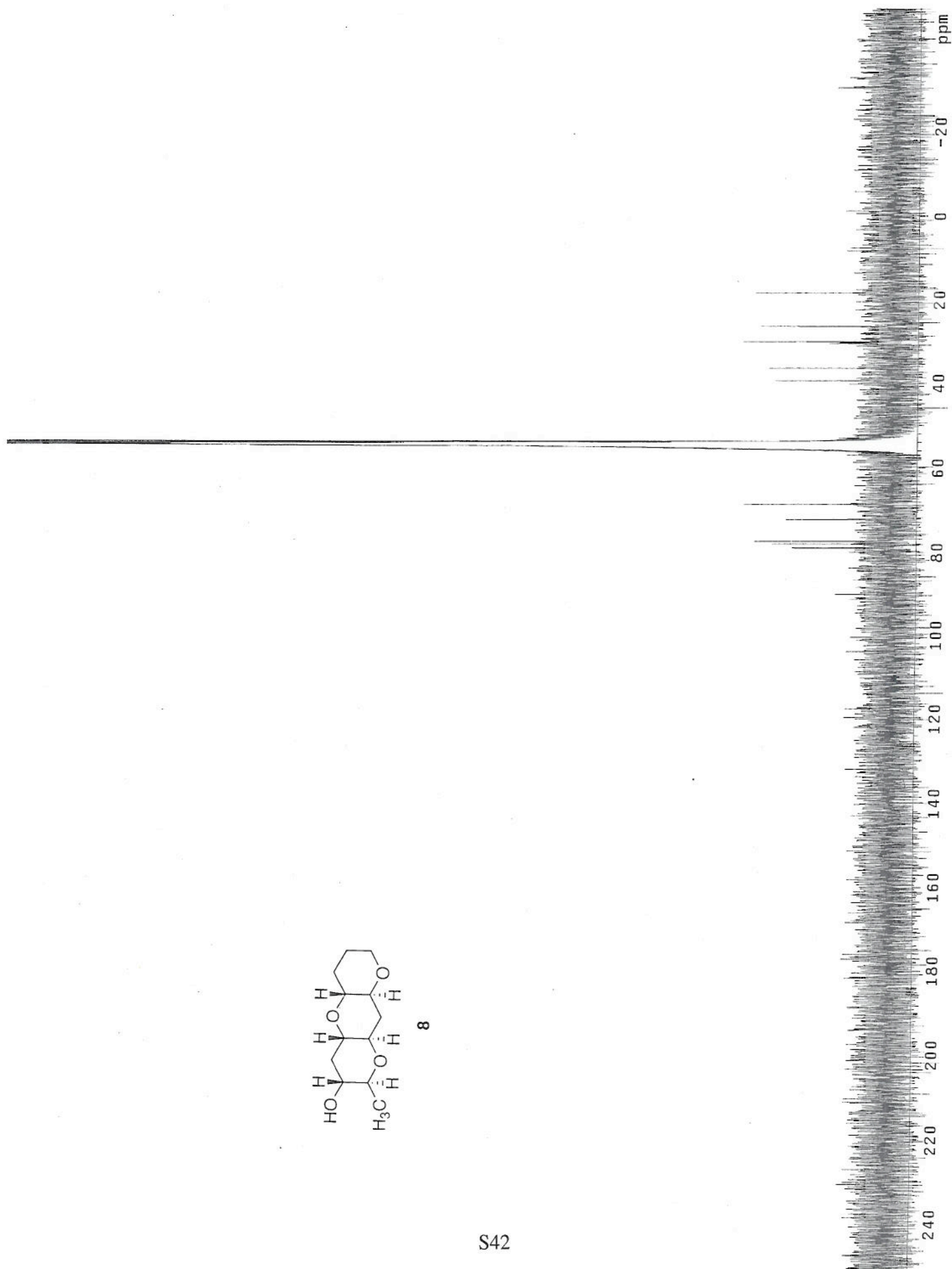


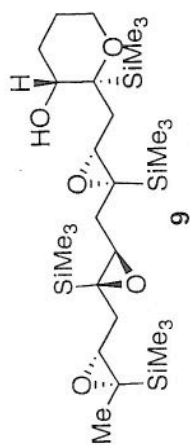
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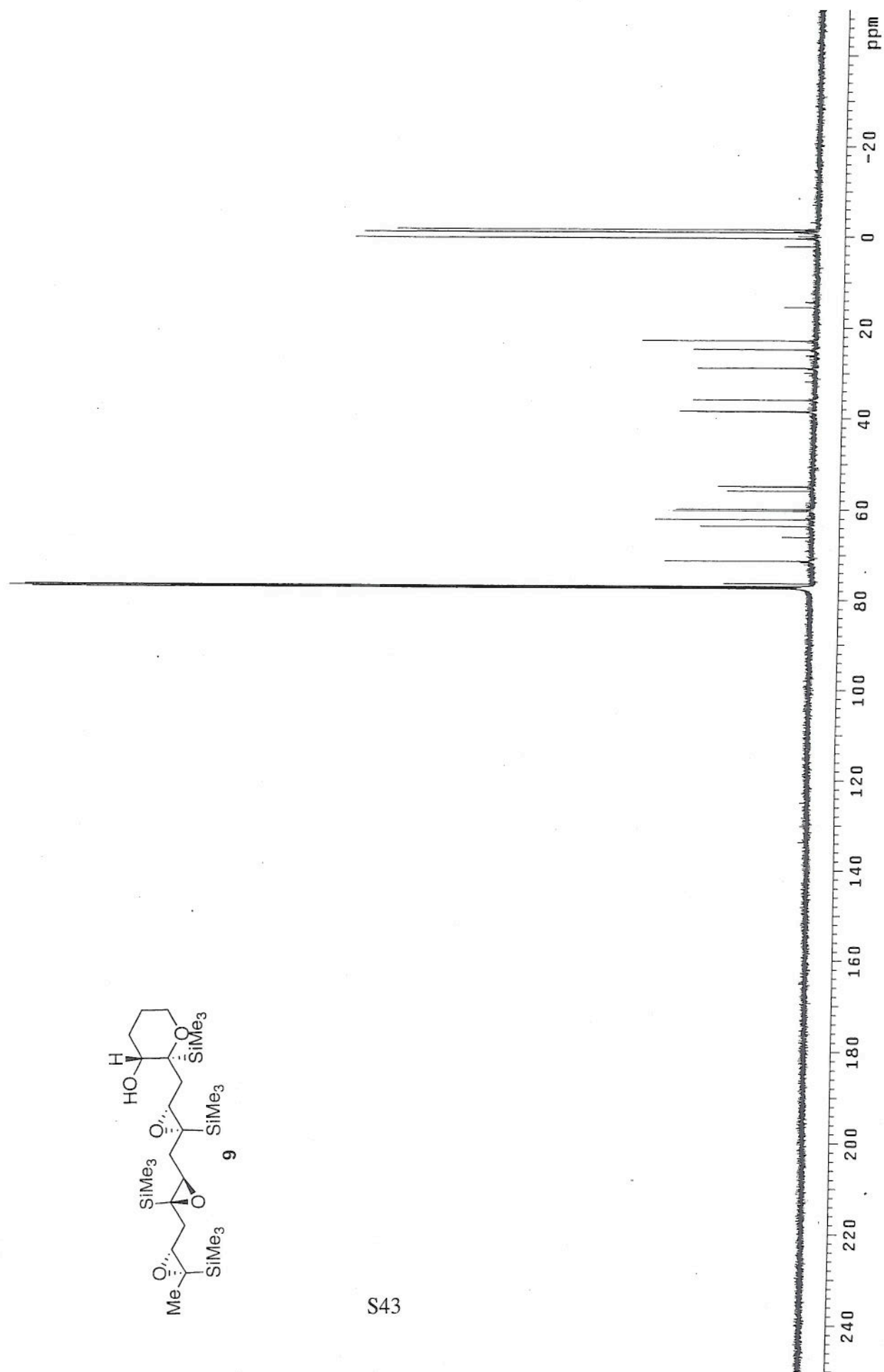


S42





S43

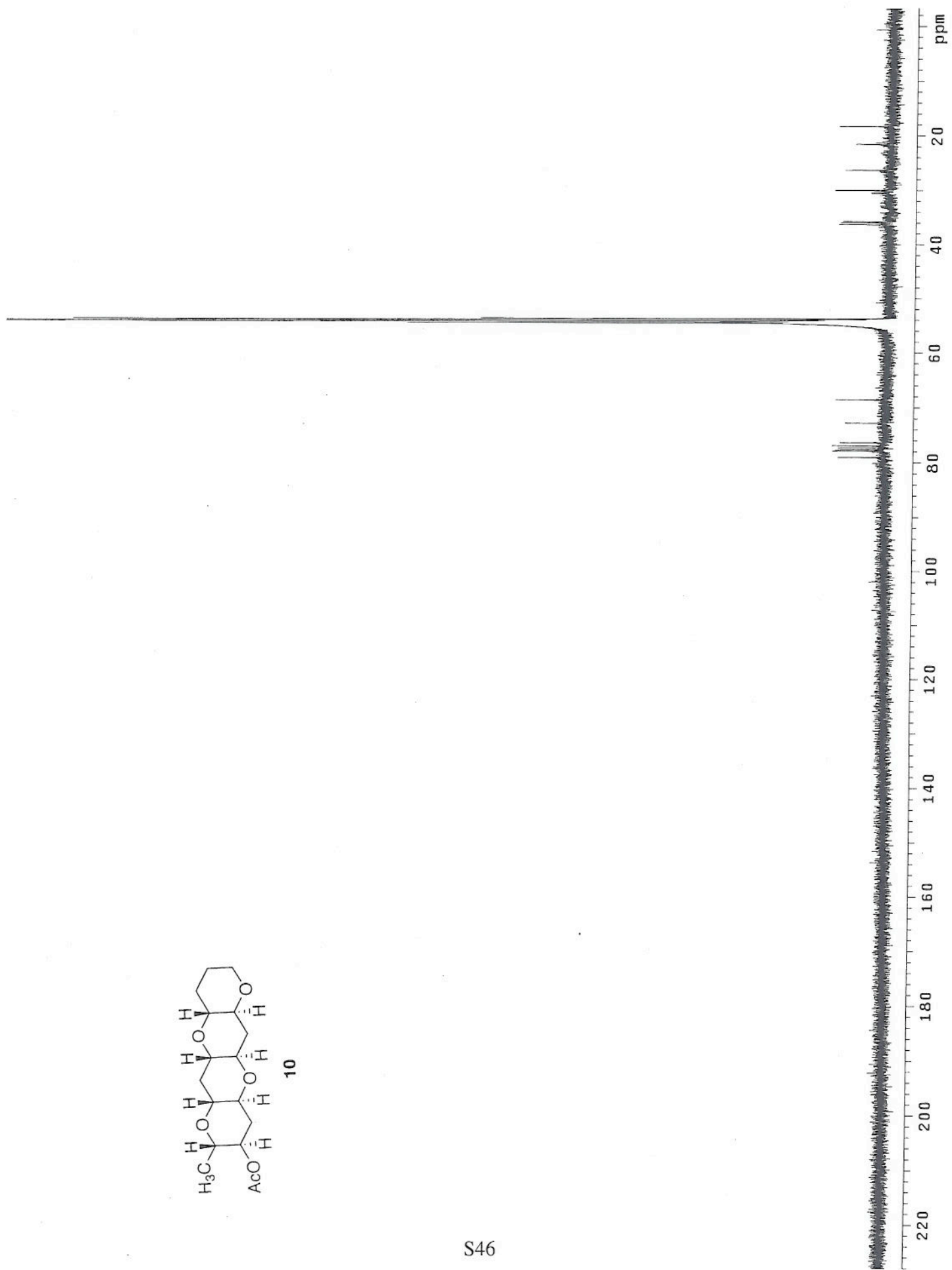
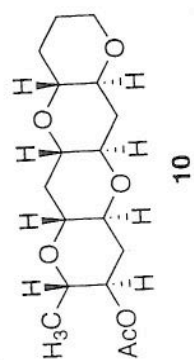


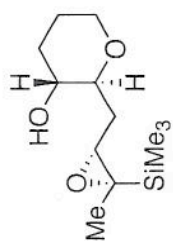




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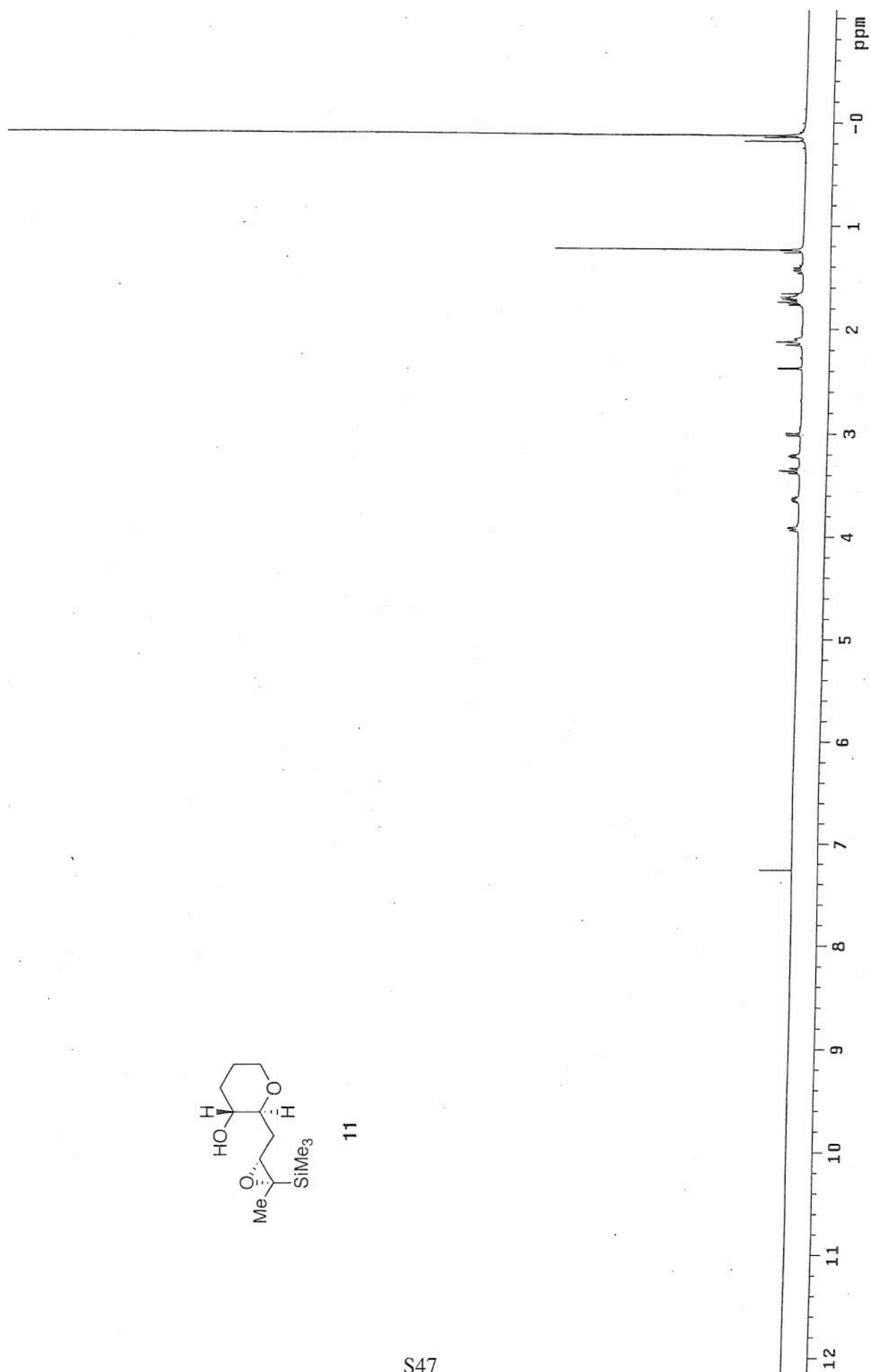


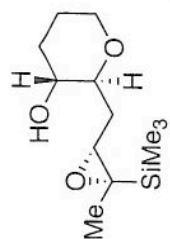




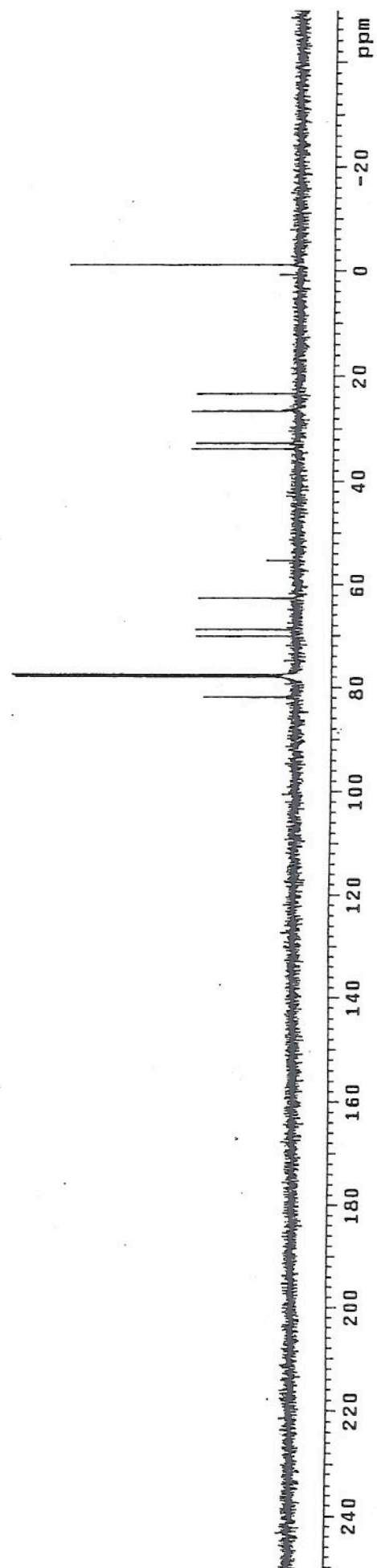
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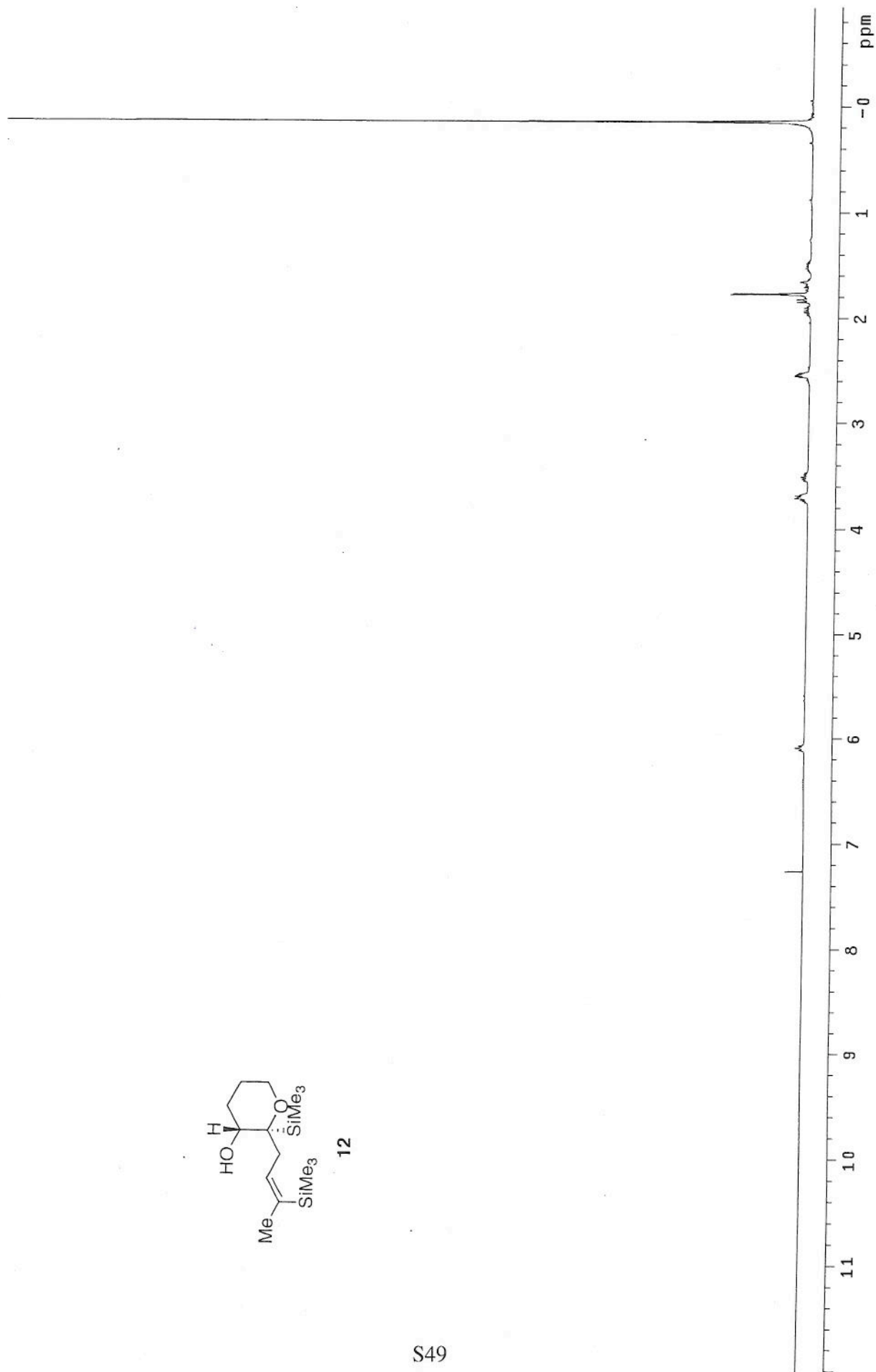
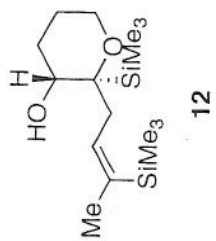


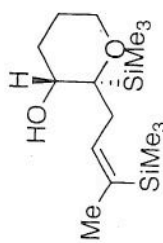


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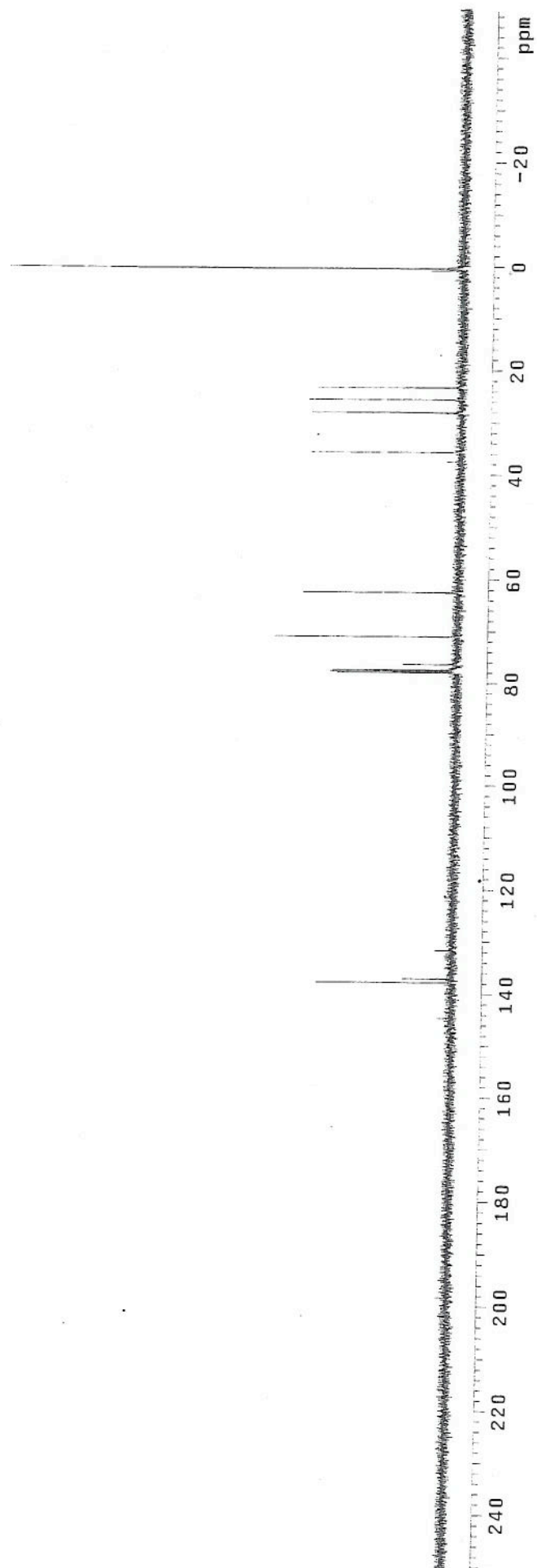




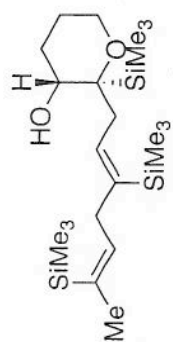


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S50

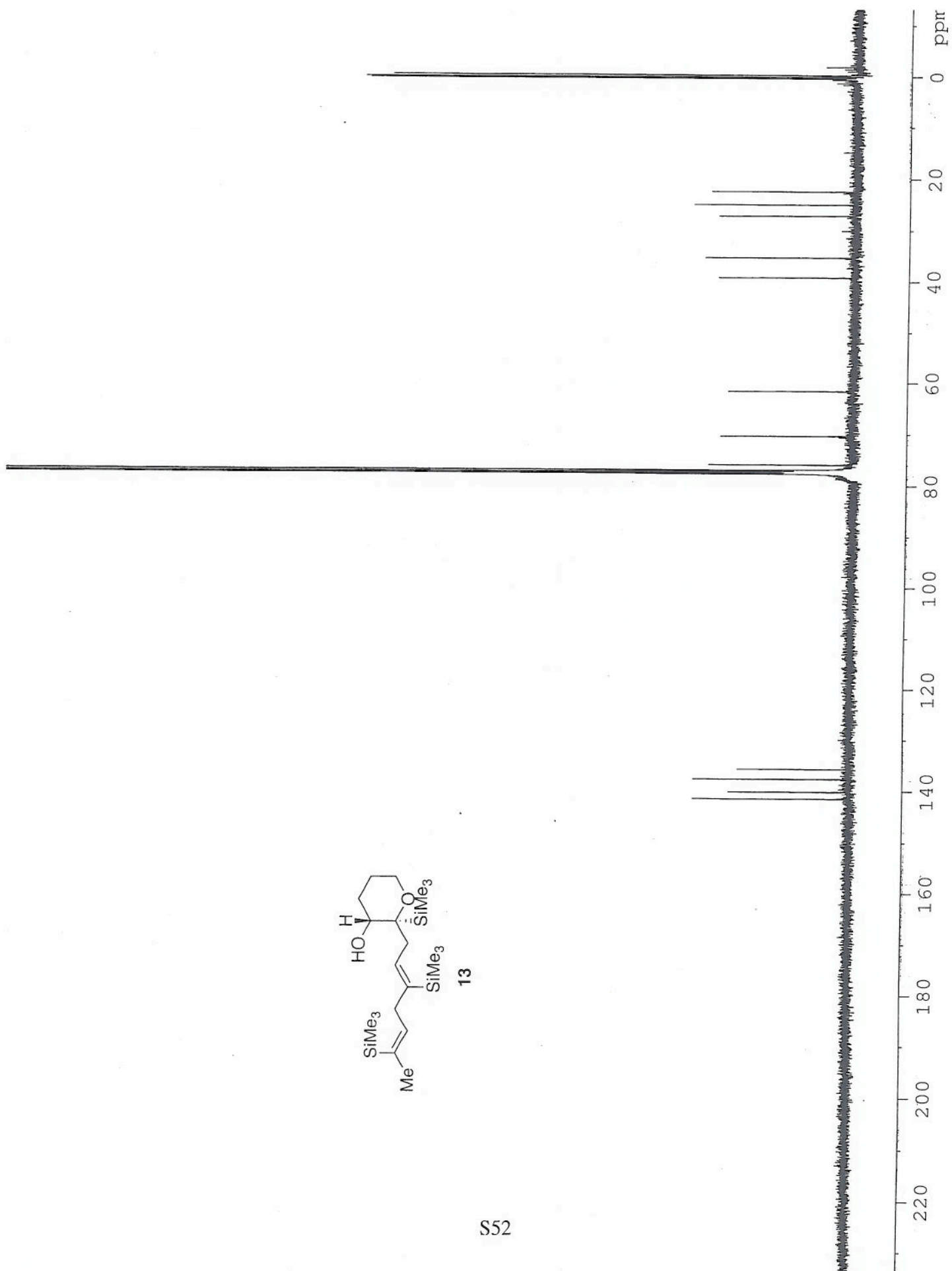






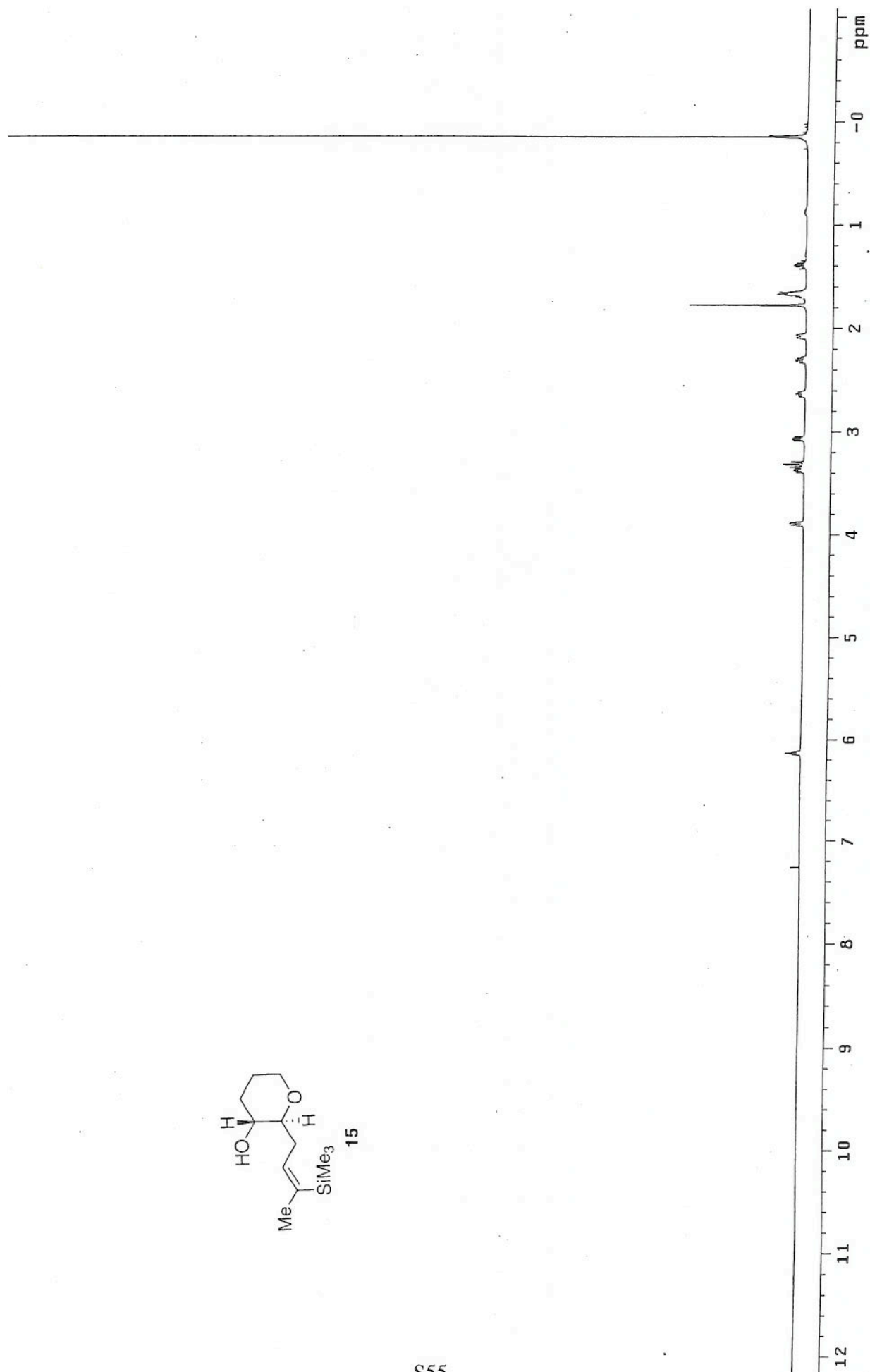
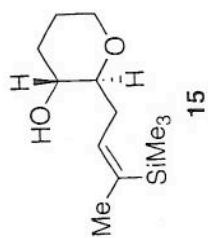
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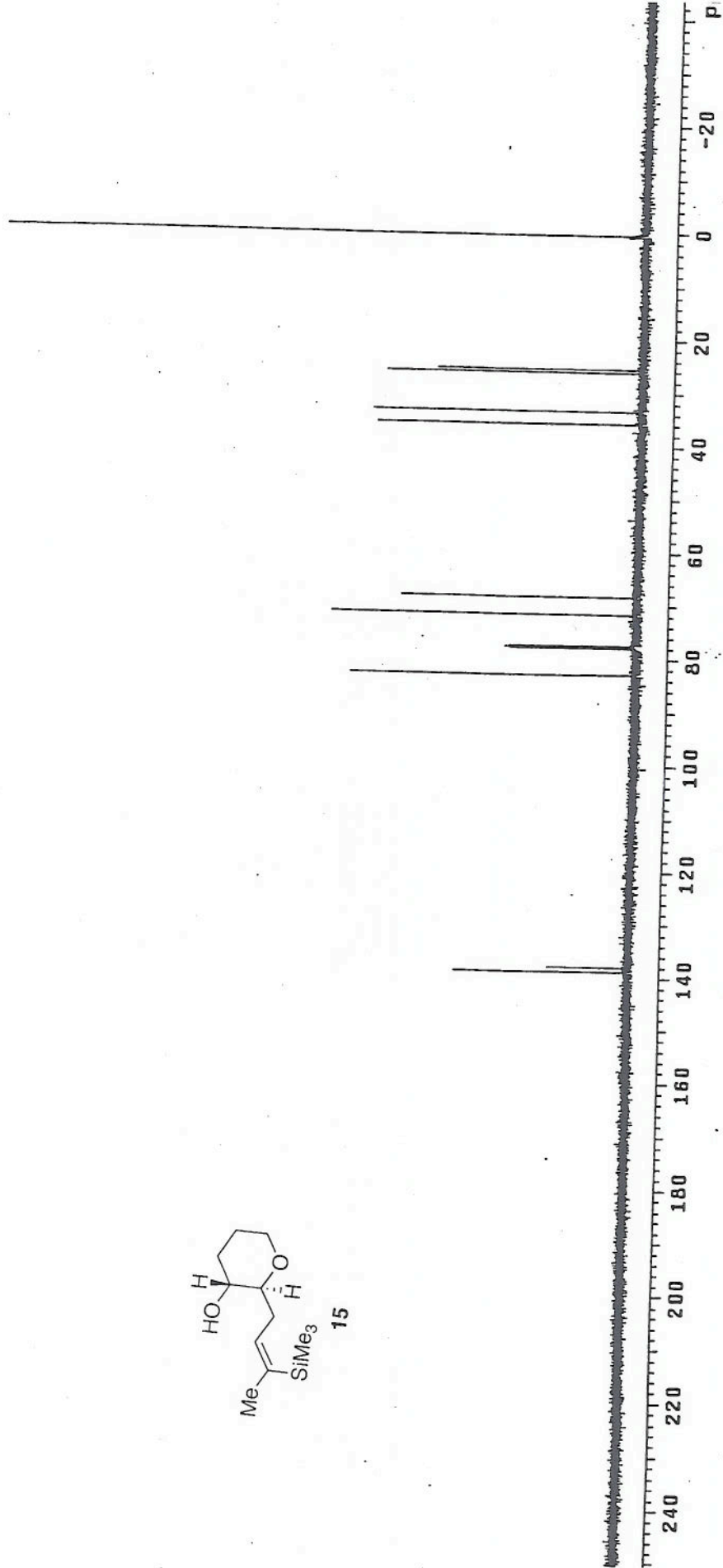
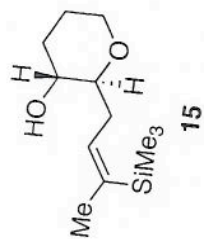
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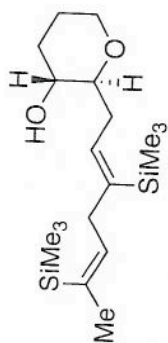






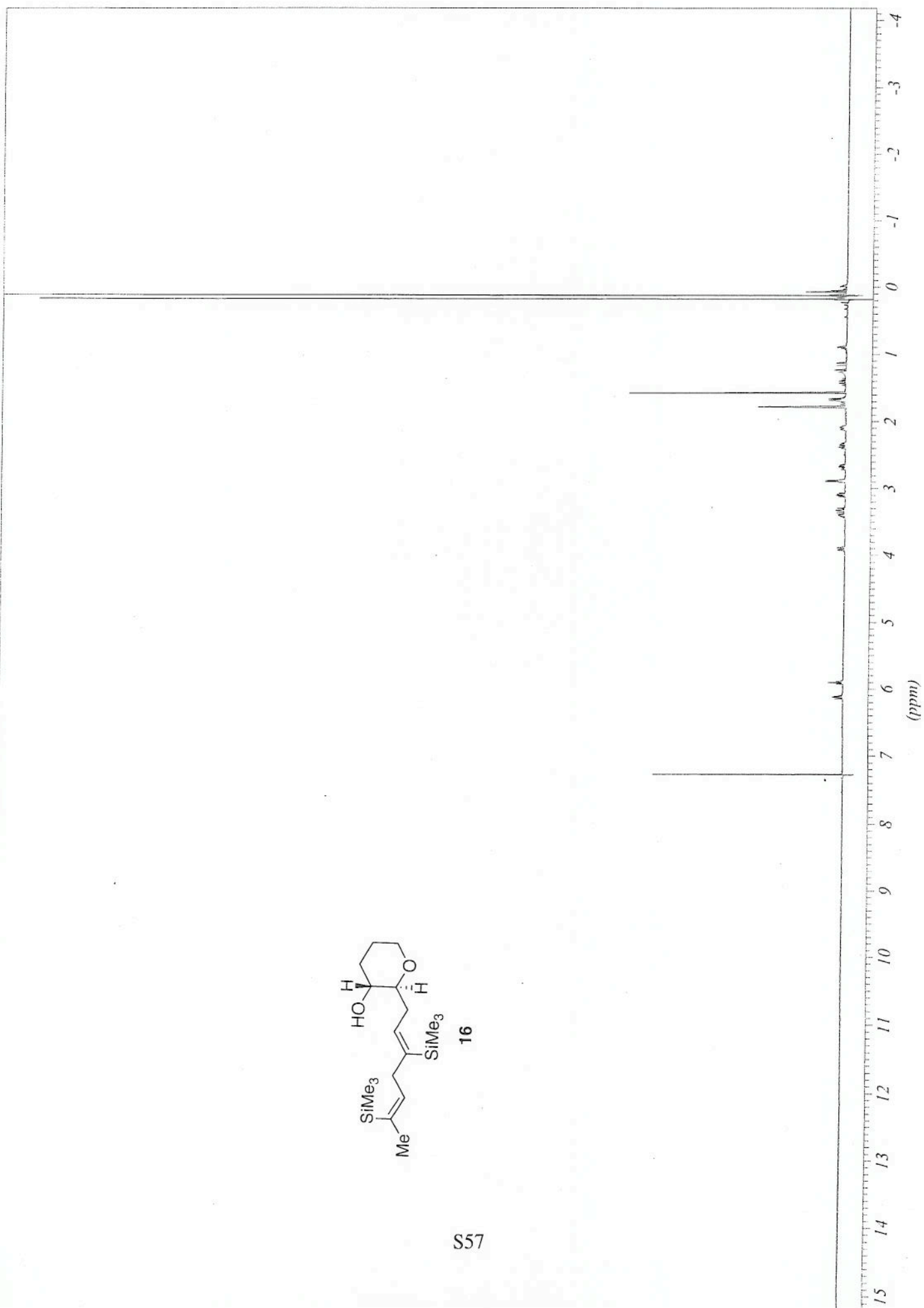




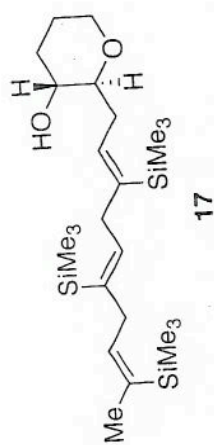


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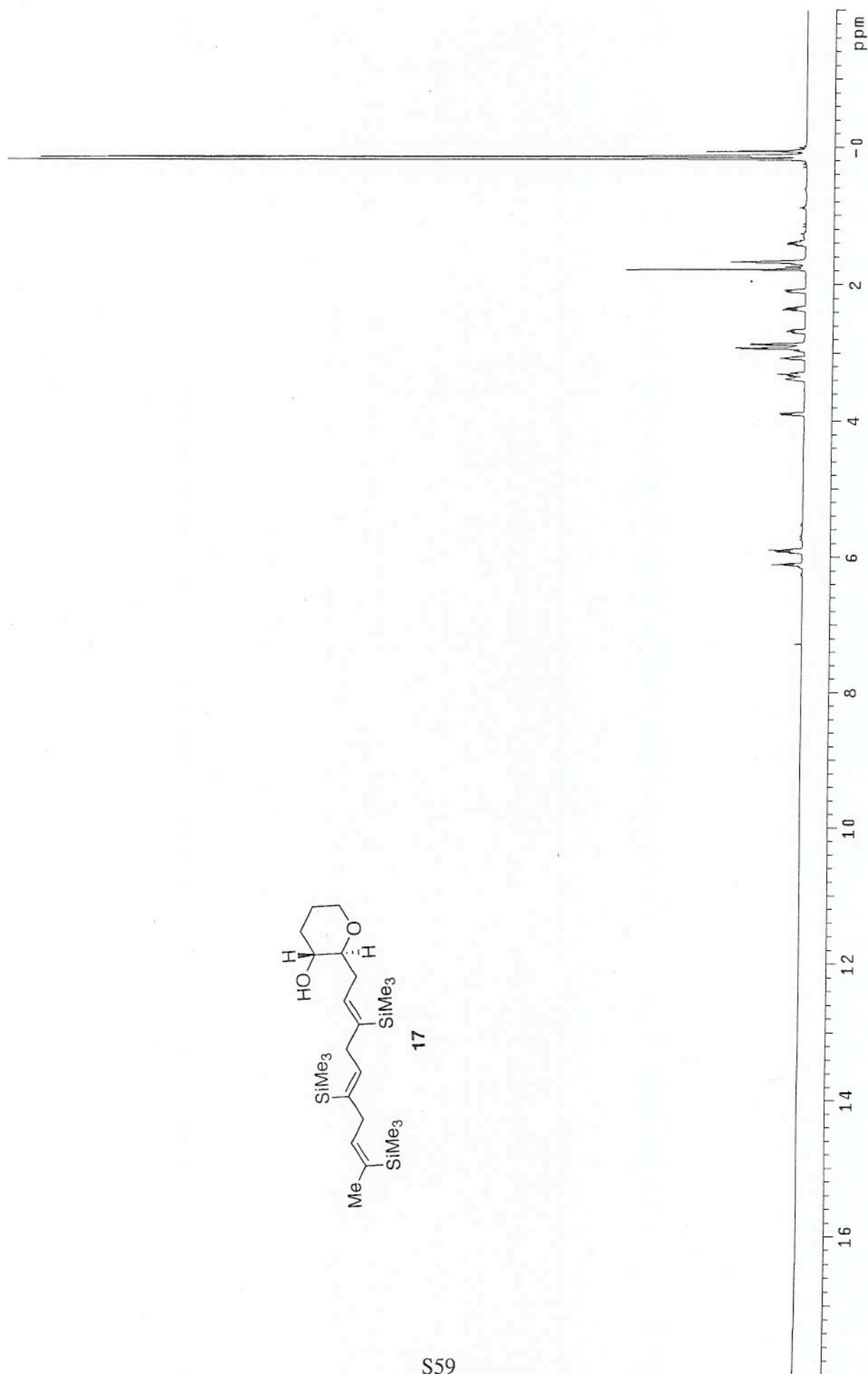
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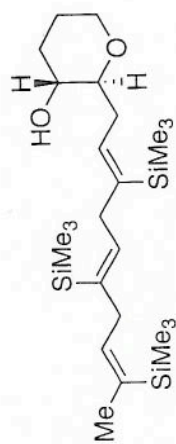






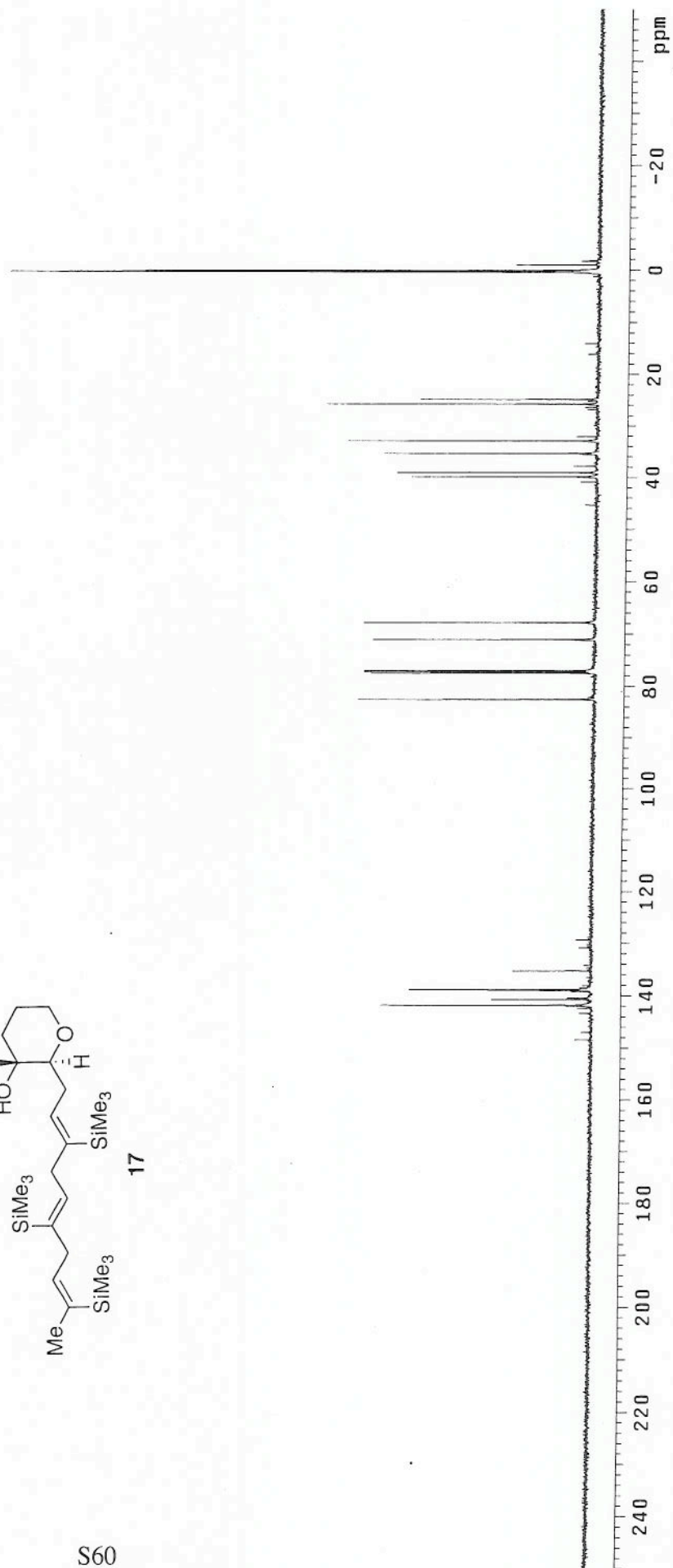
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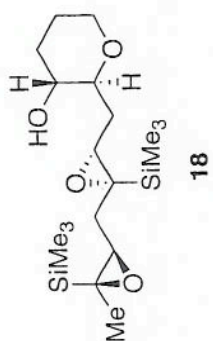




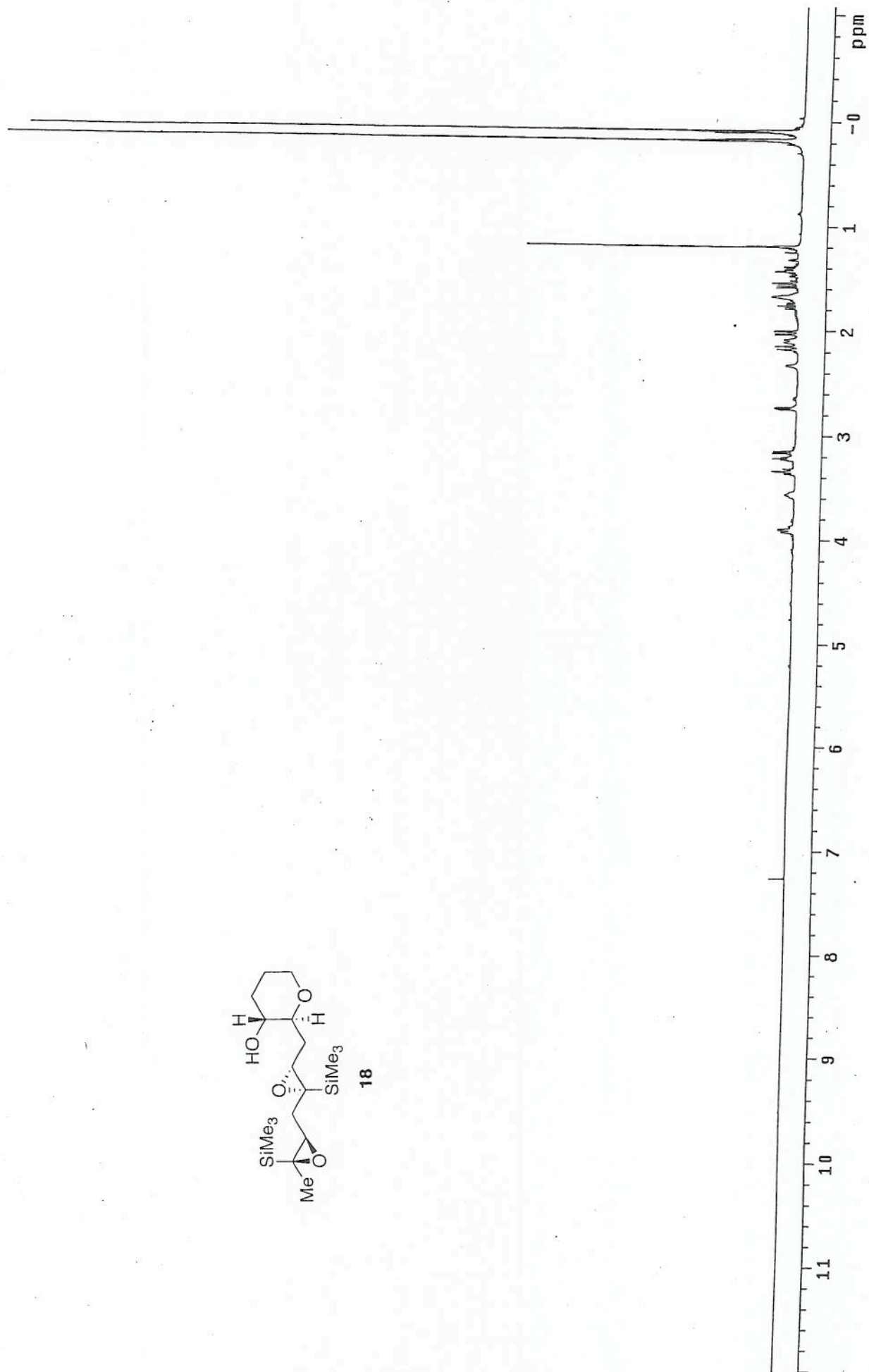
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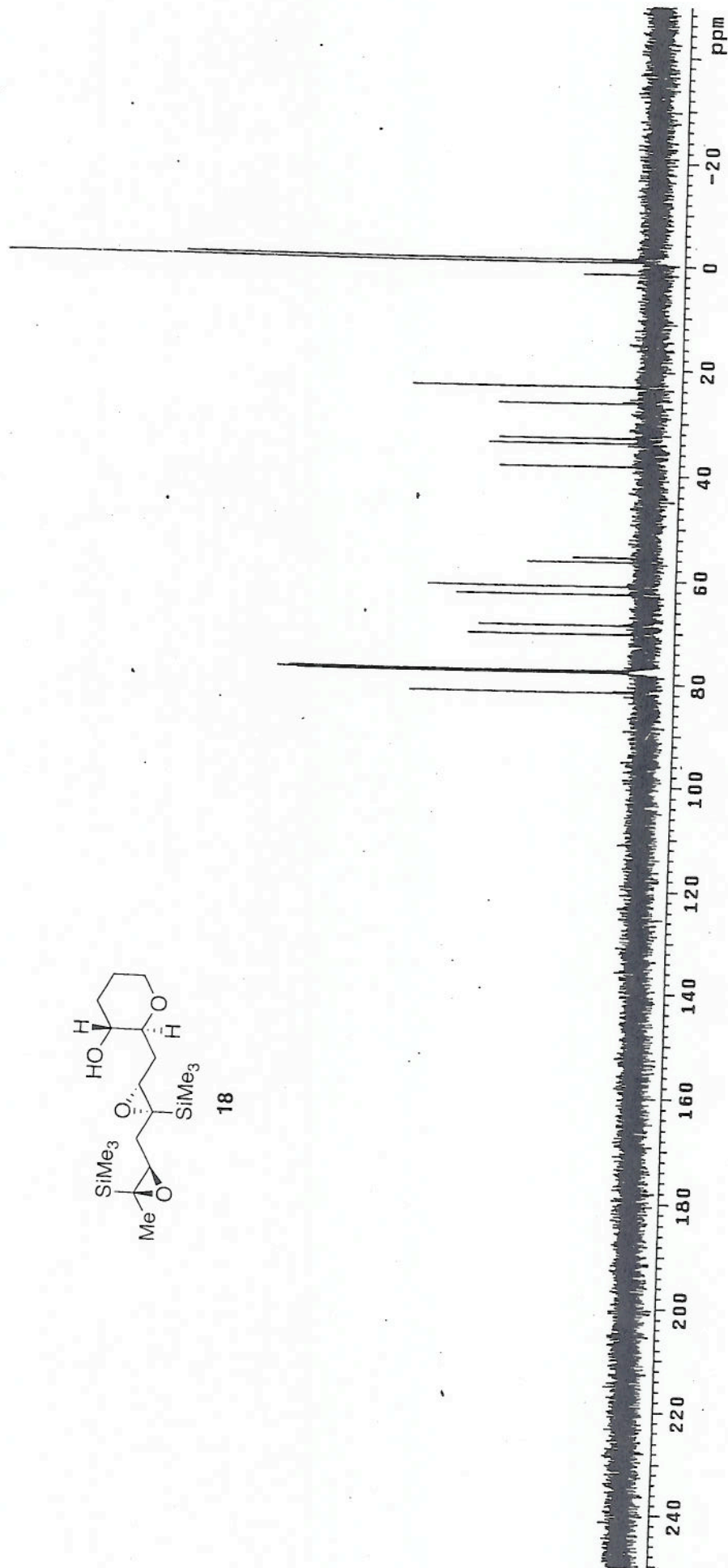
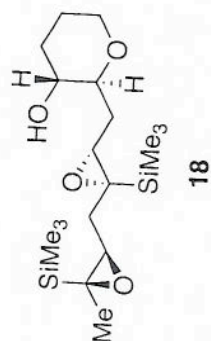
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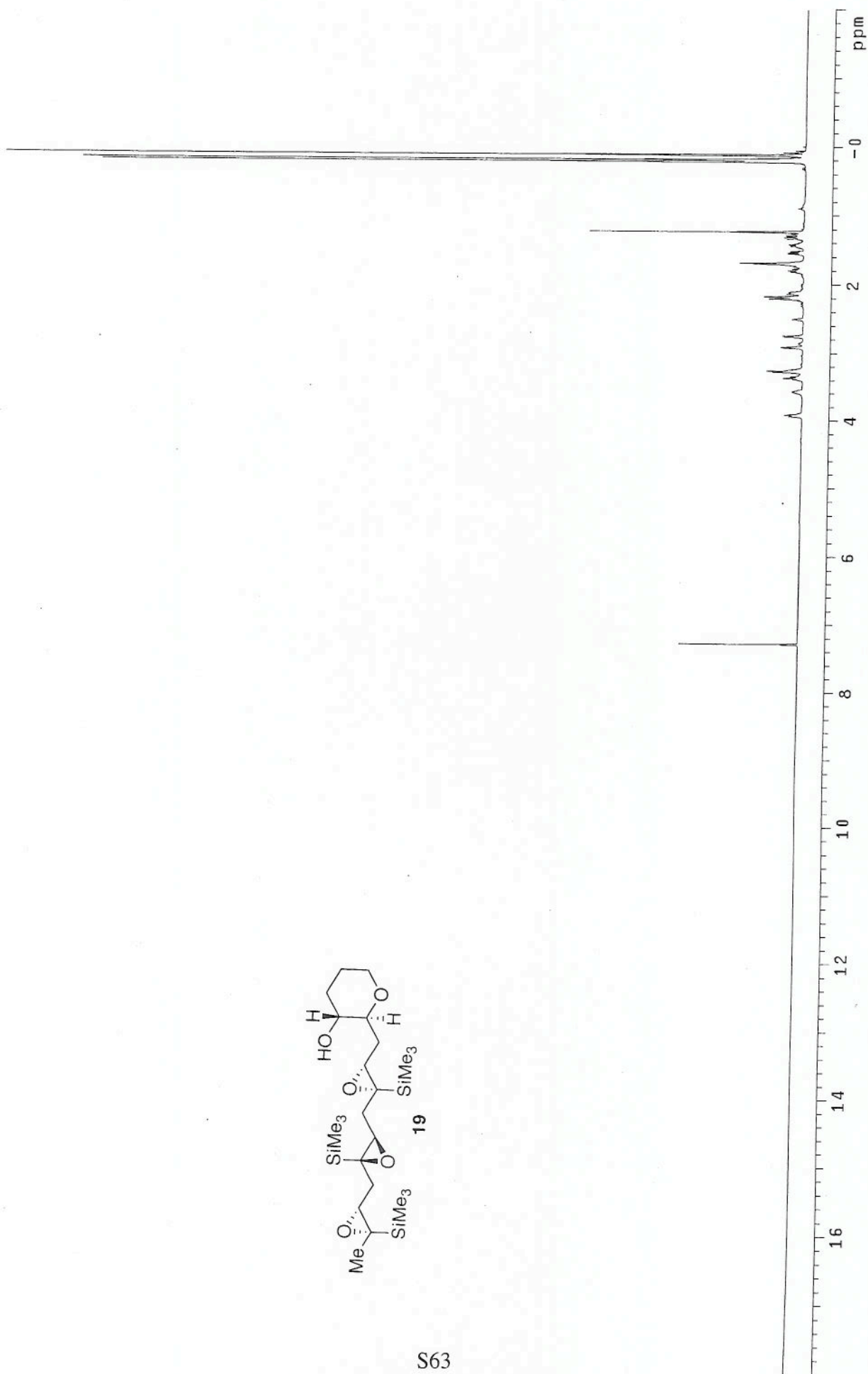
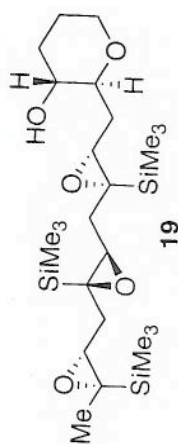


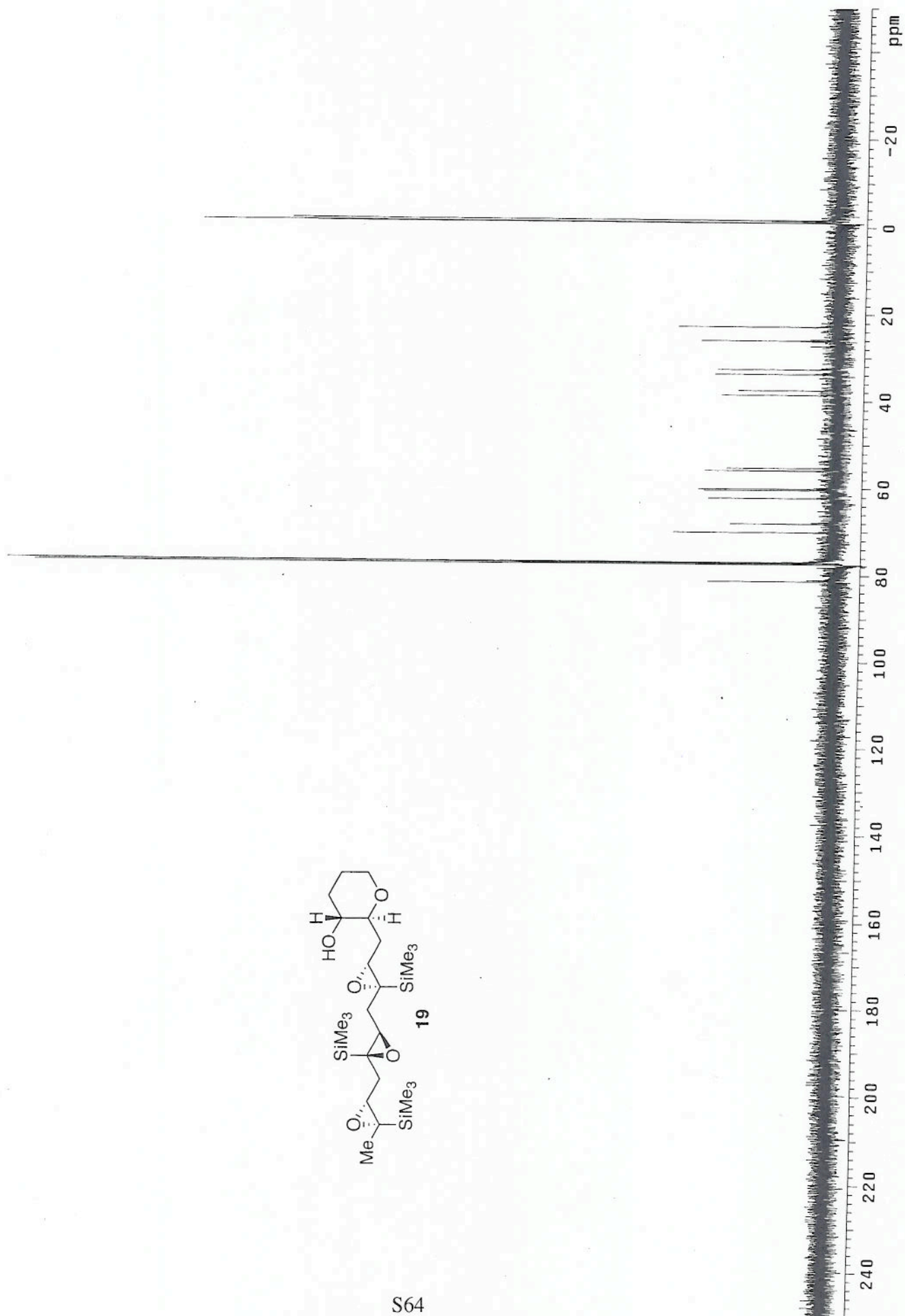
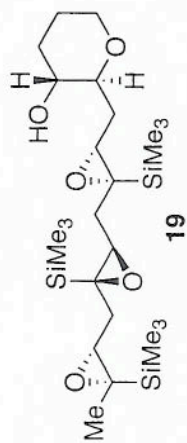


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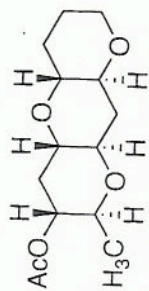






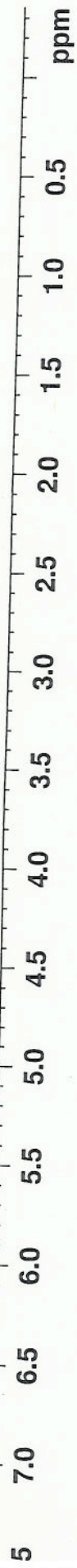


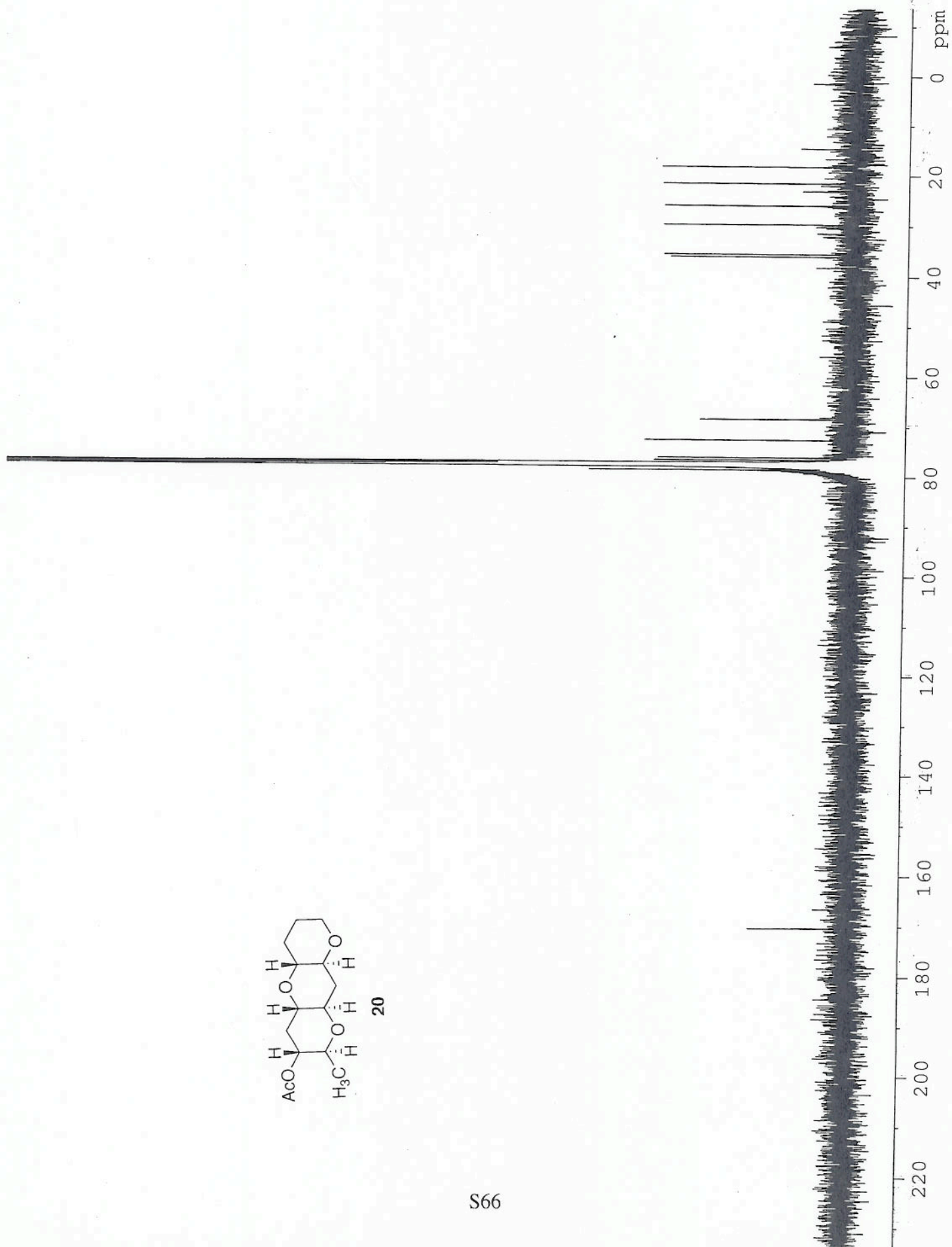
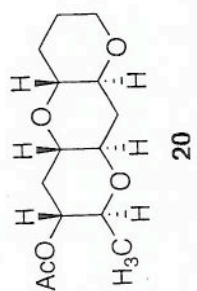




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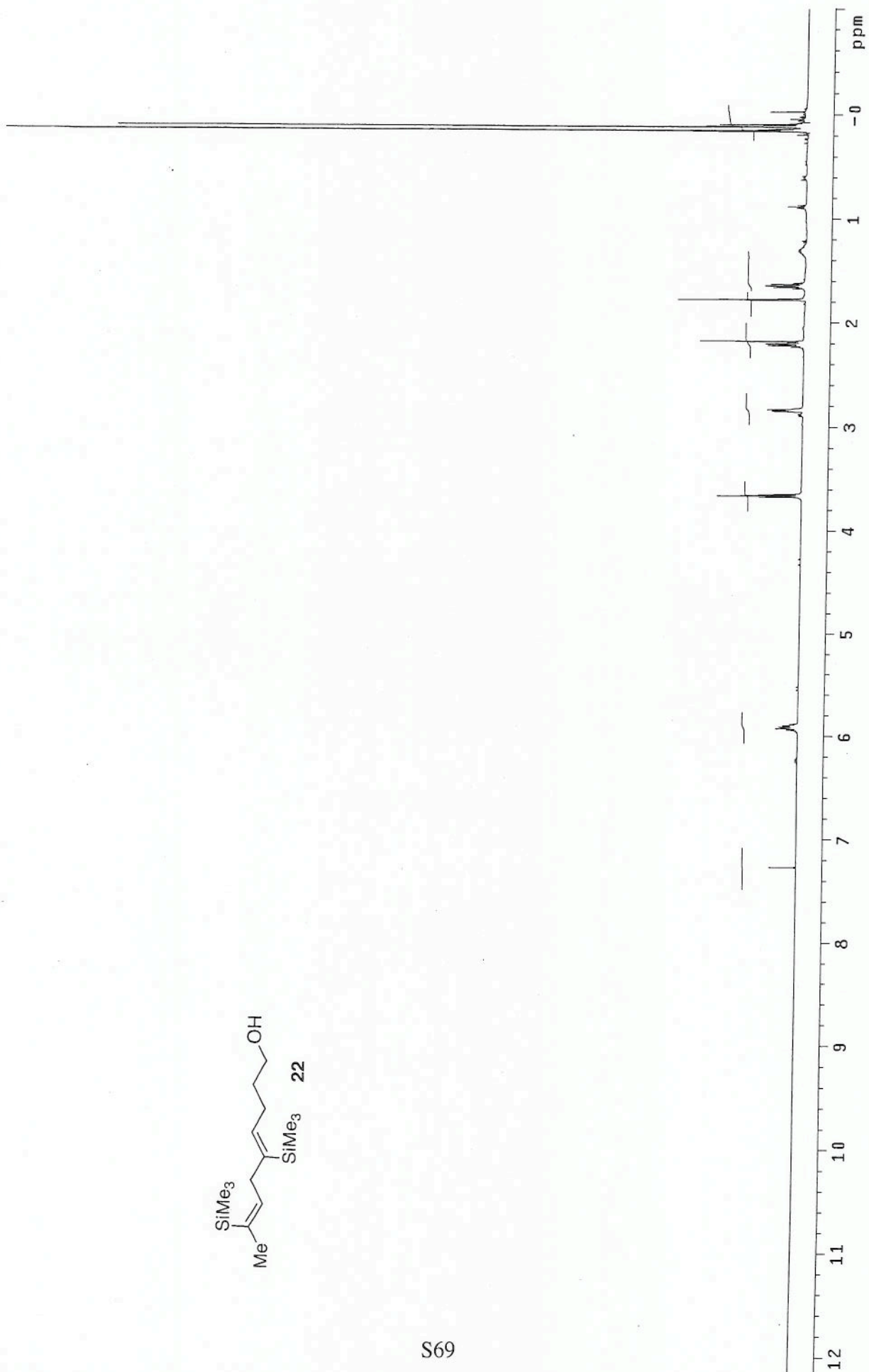
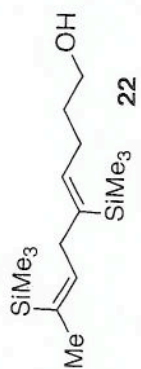
S65

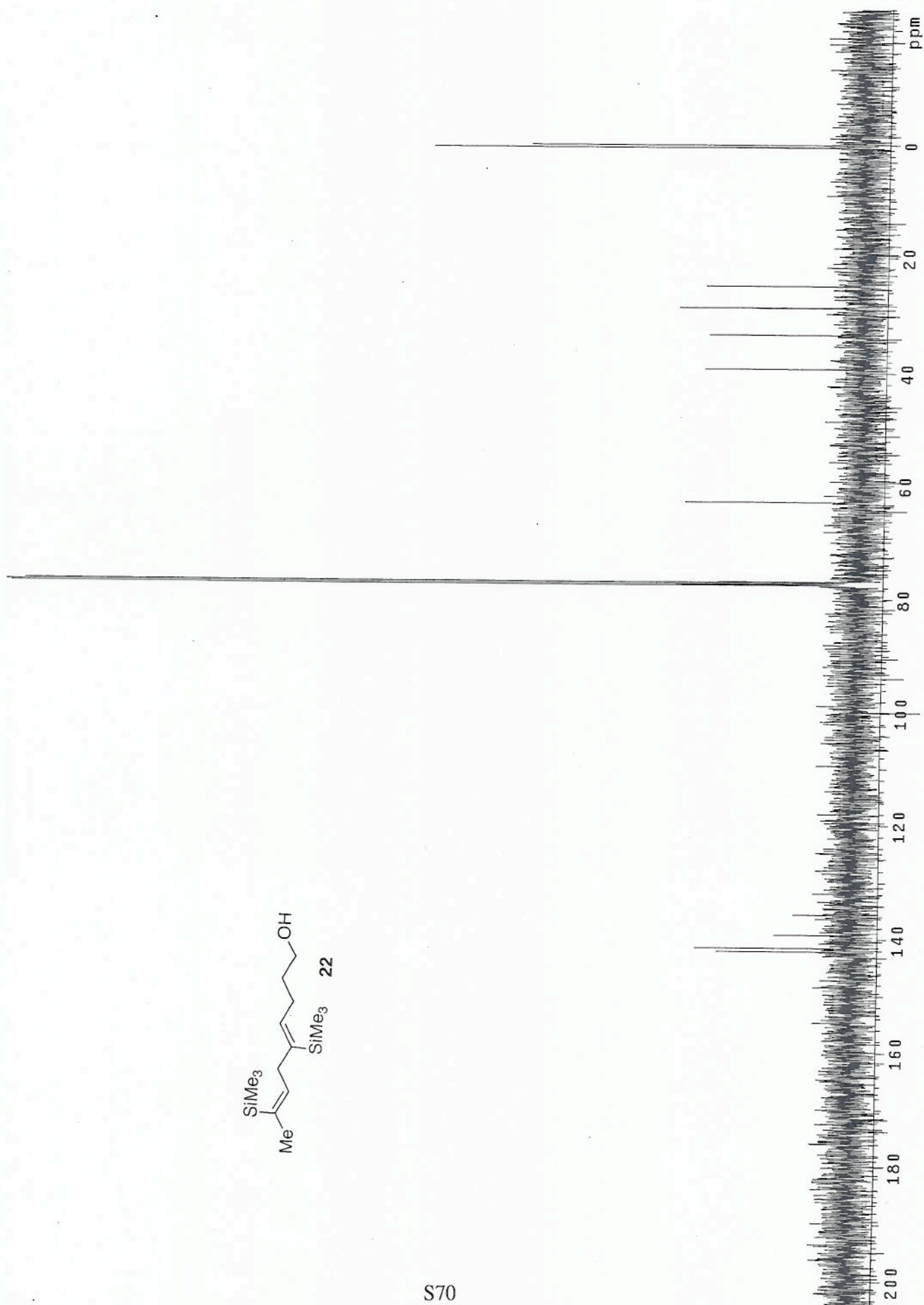
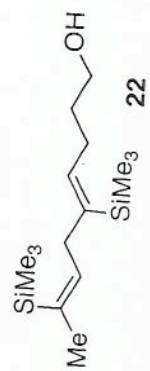




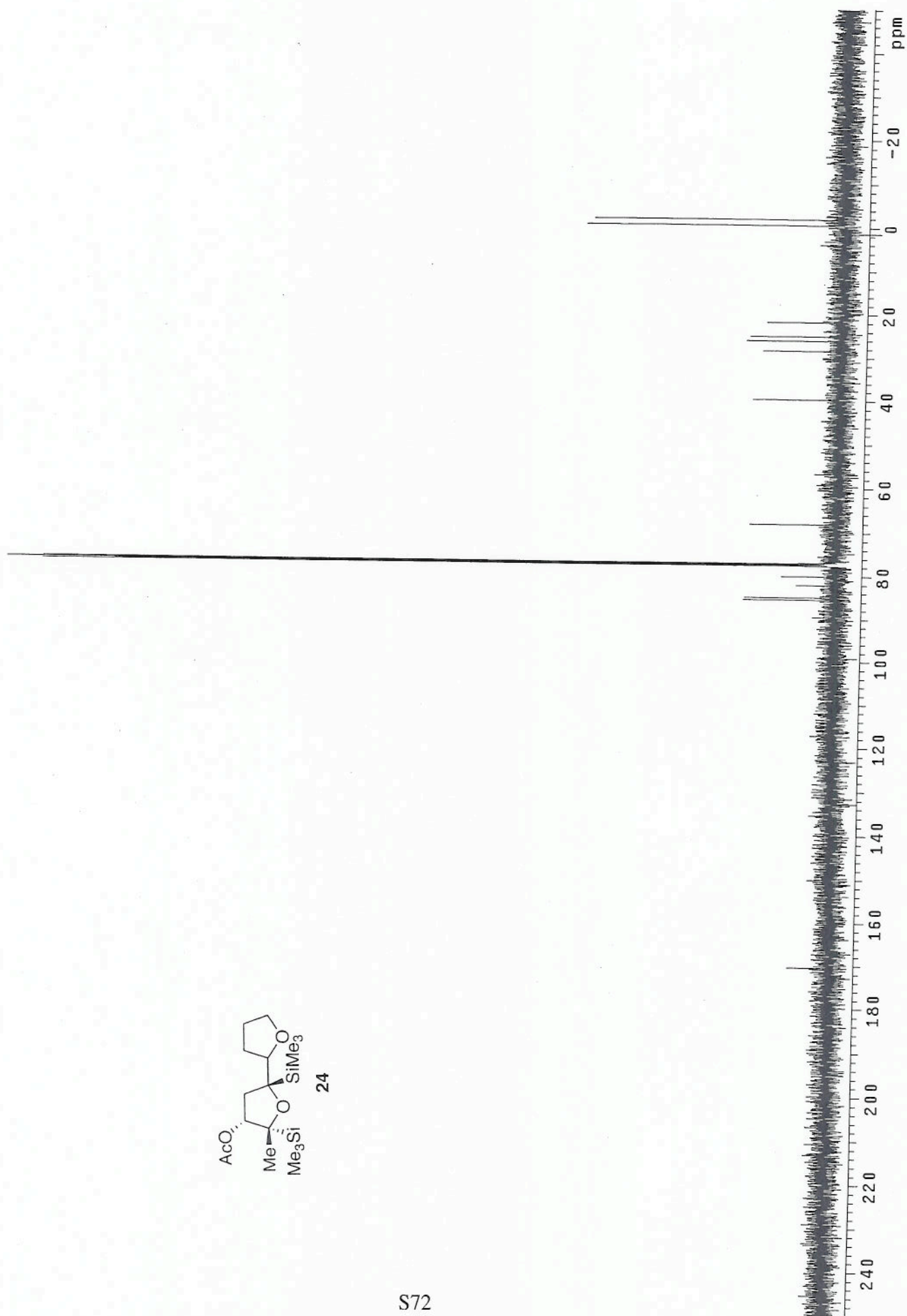
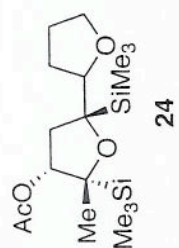




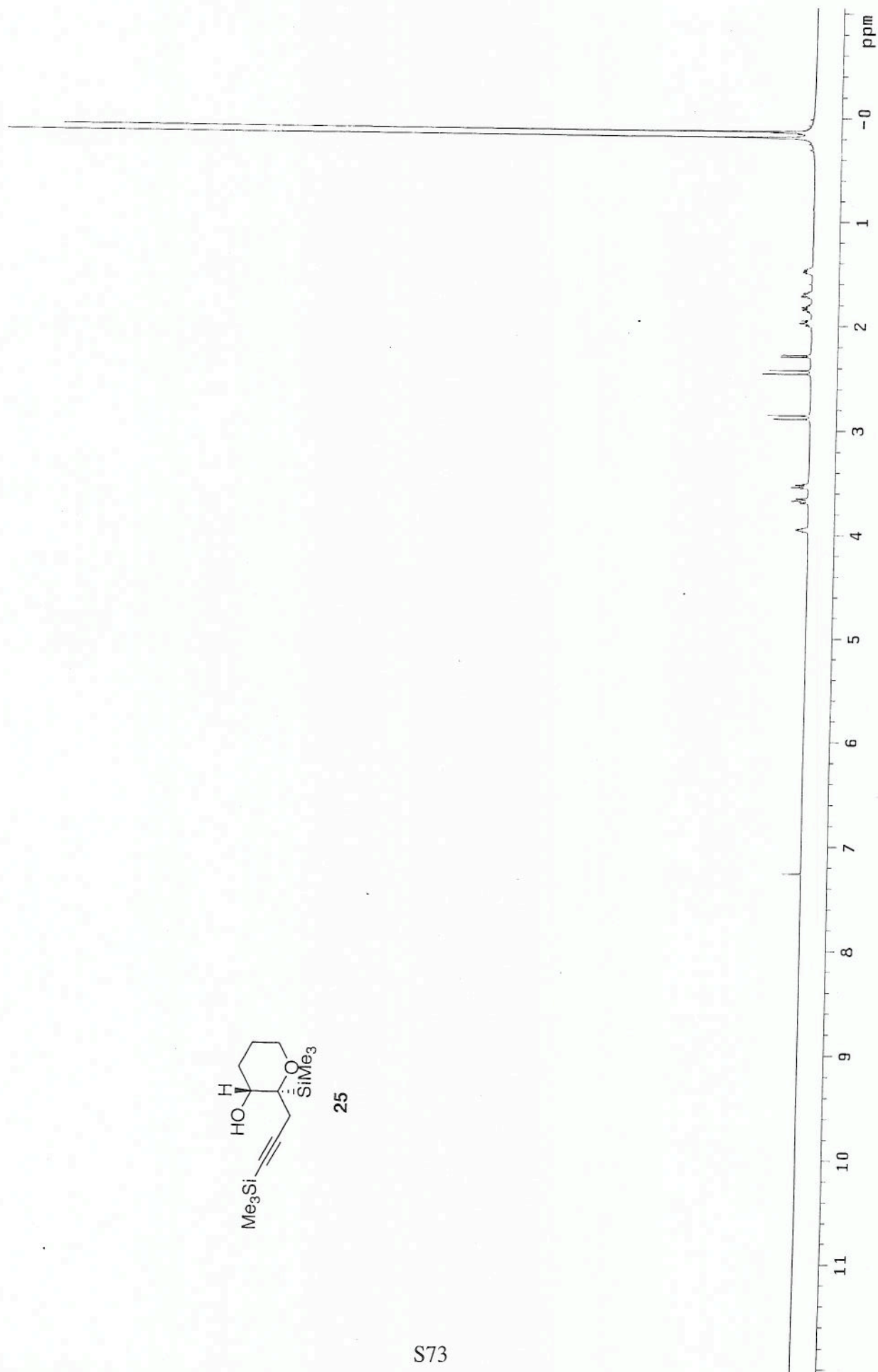
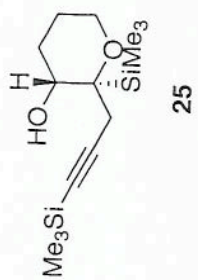


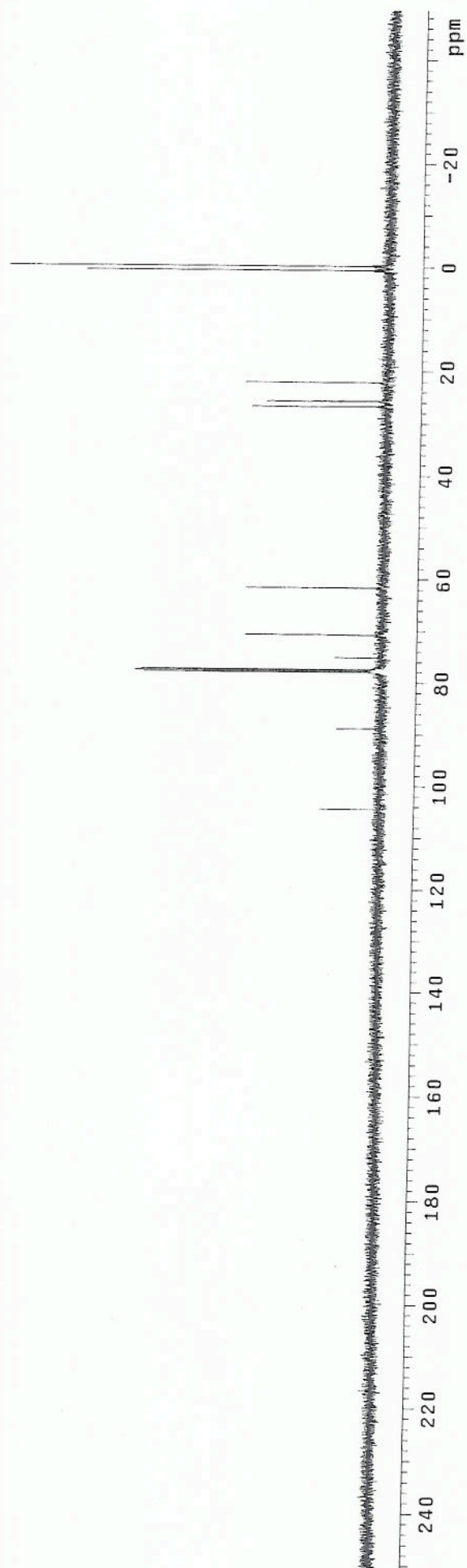
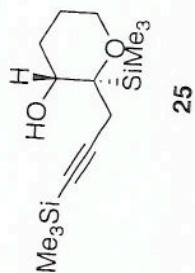


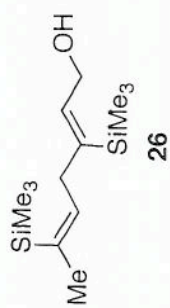








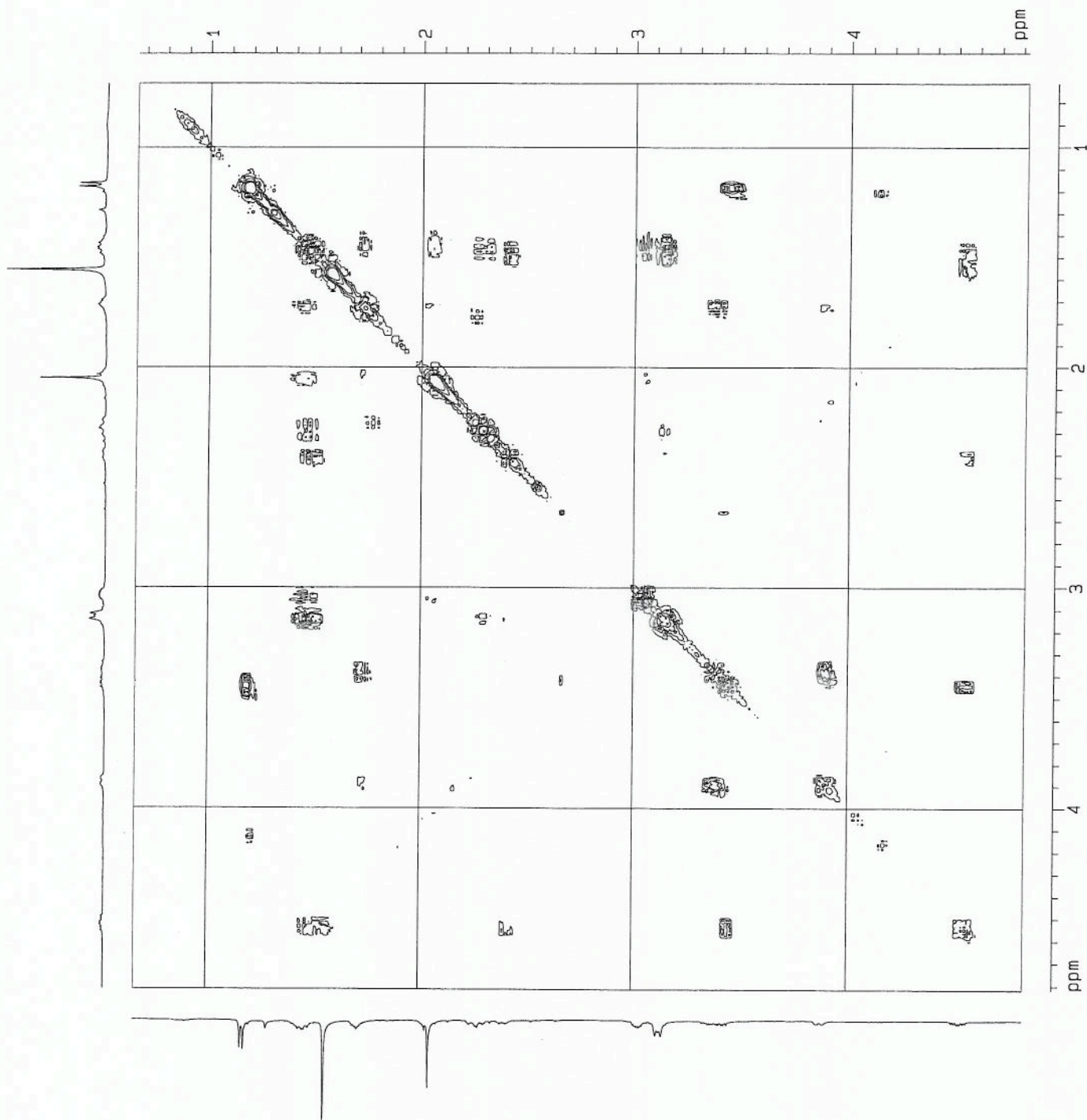
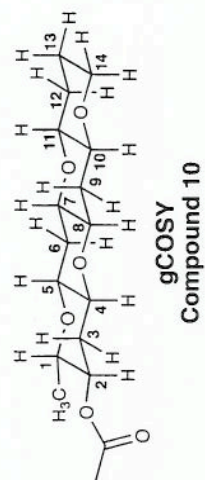




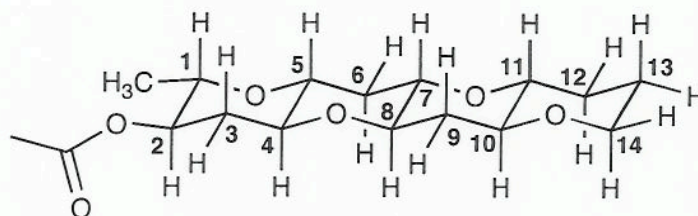
S75







Assignment of Acetylated Tetrad 10 by  $^1\text{H}$ - $^1\text{H}$  gCOSY



**gCOSY  
Compound 10**

Chemical Shift ( $\delta$ )	$^1\text{H}$ - $^1\text{H}$ gCOSY Assignment
4.52 (ddd, $J = 11.4, 9.6, 4.8$ Hz, 1H)	2ax
3.88 (m, 1H)	14eq
3.39 (m, 2H)	1ax, 14ax
3.13 (m, 4H)	4ax, 5ax, 7ax, 8ax,
3.02 (m, 2H)	10ax, 11ax
2.40 (dt, $J = 11.1, 4.2$ Hz, 1H)	3eq
2.27 (m, 2H)	6eq, 9eq
2.03 (m, 1H)	12eq
2.05 (s, 3H)	Ac
1.72 (m, 2H)	13ax, 13eq
1.44 (m, 4H)	3ax, 6ax, 9ax, 12ax
1.17 (d, $J = 6.1$ Hz, 3H)	Me