"Highly Selective Catalytic Intermolecular Reductive Coupling of Alkynes"

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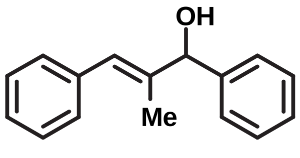
Supporting Information

General. Ni(COD)$_2$ was purchased from Strem Chemicals, Inc. and used without further purification. Tributylphosphine (97%, catalog number 24,704-9) and triethylborane (1.0 M solution in hexanes) were purchased from Aldrich Chemical Co. and used without further purification. All alkynes and aldehydes were purchased from Aldrich Chemical Co. or Alfa Aesar and used without further purification. Toluene and tetrahydrofuran were distilled from a blue solution of sodium benzophenone ketyl under an atmosphere of N$_2$ or Ar immediately prior to use.

Standard Experimental Procedure for Intermolecular Reductive Coupling of Alkynes and Aldehydes

In a glovebox, Ni(COD)$_2$ (28 mg, 0.10 mmol) was placed into an oven-dried, one-necked Schlenk flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, and toluene (2 mL (degassed with Ar or N$_2$ by three freeze-pump-thaw cycles) was added via syringe. To this yellow solution Bu$_3$P (0.050 mL, 0.20 mmol) was added via syringe, and the resulting solution was stirred 5 min at ambient temperature. Et$_3$B (2.0 mL, 1.0 M in hexanes, 2.0 mmol) was added via syringe, and the resulting mixture was stirred 10-15 min. A solution of the alkyne (1.0 mmol) and aldehyde (1.0 mmol) in toluene (2 mL, degassed with Ar or N$_2$ by three freeze-pump-thaw cycles) was added dropwise via syringe over 1 min. The resulting solution turned brown in 5-10 min and was stirred at ambient temperature 18 h unless otherwise indicated. Saturated aqueous NH$_4$Cl (4 mL) and 1 N HCl (1 mL) were added, and the resulting mixture was diluted with water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic solutions were washed with saturated aqueous NaCl and then dried over Na$_2$SO$_4$. After filtration and removal of the solvent in vacuo, the allylic alcohol was purified by silica gel chromatography using hexanes:ethyl acetate (15:1 to 5:1) as eluent.



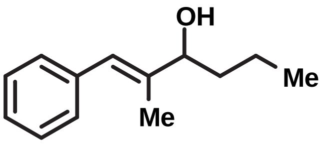
3a

***(E)*-1,3-diphenyl-2-methyl-2-propen-1-ol (3a**, Table 2, entry 1). In the reductive coupling of 1-phenylpropyne (**1a**, 1.0 mmol, 0.13 mL) and benzaldehyde (**2a**, 1.0 mmol, 0.10 mL) the standard procedure was used. Silica gel chromatography afforded allylic alcohols **3a** and **3b** as a colorless oil (173 mg, 77%). R_f = 0.41 (5:1 hexanes:ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 10H), 6.72 (s, 1H), 5.85 (q, *J* = 6.9, 0.09H, minor regioisomer), 5.37 (s, 0.09H, minor regioisomer), 5.22 (s, 1H), 1.94 (br s, 1H), 1.67 (d, *J* = 1.5, 3H).

^{13}C NMR (75.40 MHz, $CDCl_3$) δ 142.20, 139.70, 137.63, 129.21, 128.60, 128.31, 127.79, 126.73, 126.64, 126.14, 79.66, 14.23.

Spectral data were identical with those previously reported.[1]



4a

***(E)*-2-methyl-1-phenyl-1-hexen-3-ol (4a**, Table 2, entry 2). In the reductive coupling of 1-phenylpropyne (**1a**, 1.0 mmol, 0.13 mL) and butyraldehyde (**2b**, 2.0 mmol, 0.18 mL), the standard procedure was used except that 200 mol% butyraldehyde was used. Silica gel chromatography afforded allylic alcohols **4a** and **4b** as a colorless oil (162 mg, 85%). R_f = 0.46 (5:1 hexanes:ethyl acetate).

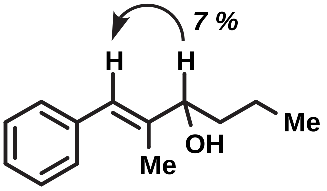
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.08 (m, 5H), 6.38 (s, 1H), 5.69 (qd, *J* = 6.9, 0.9, 0.08H, minor regioisomer), 4.20 (m, 0.08H, minor regioisomer), 4.07 (t, *J* = 6.3, 1H), 1.88 (br s, 1H), 1.77 (d, *J* = 1.2, 3H), 1.54 (dt, *J* = 6.9, 7.2, 2H), 1.44 – 1.19 (m, 2H), 0.87 (t, *J* = 7.2, 3H).

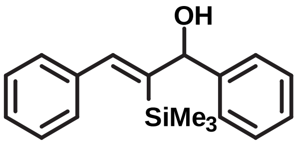
^{13}C NMR (75.40 MHz, $CDCl_3$) δ 140.61, 137.78, 129.14, 128.28, 126.58, 125.90, 78.14, 37.44, 19.23, 14.23, 13.30.

IR (film, CH_2Cl_2): 3401, 2967, 2869, 1700, 1658, 1491, 1449, 990 cm^{-1}.

LRMS (EI) m/e calcd (M^+): 190, found 190.

Irradiation of the carbinol methine proton resulted in a 7% nOe of the alkene proton, consistent with an *E* olefin geometry in the major allylic alcohol regioisomer:





5a

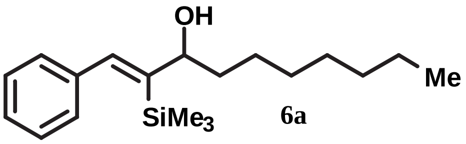
***(Z)*-1,3-diphenyl-2-(trimethylsilyl)-2-propen-1-ol (5a**, Table 2, entry 3). In the reductive coupling of 1-phenyl-2-(trimethylsilyl)acetylene (**1b**, 1 mmol, 0.20 mL) and benzaldehyde (**2a**, 1.0 mol, 0.10 mL), the standard procedure was used. Silica gel chromatography afforded **5a** as a colorless oil (138 mg, 49%). R_f = 0.52 (5:1 hexanes:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59 (s, 1H), 7.47 – 7.26 (m, 10H), 5.51 (s, 1H), 2.15 (s, 1H), –0.14 (s, 9H).

^{13}C NMR (75.40 MHz, CDCl$_3$) δ 145.66, 143.00, 141.48, 140.23, 128.73, 128.60, 128.01, 127.92, 127.82, 127.22, 78.08, 0.86.

IR (film, CH$_2$Cl$_2$): 3397, 3059, 2953, 2896, 1594, 1491, 1454, 1248, 1064, 840, 740 cm^{-1}.

LRMS (EI) m/e calcd (M$^+$): 282, found 282.



6a

***(Z)*-1-phenyl-2-(trimethylsilyl)-1-decen-3-ol (6a**, Table 2, entry 4). In the reductive coupling of 1-phenyl-2-(trimethylsilyl)acetylene (**1b**, 1.0 mmol, 0.20 mL) and octanal (**2c**, 1.0 mmol, 0.16 mL), the standard procedure was used. Silica gel chromatography afforded **6a** as a colorless oil (270 mg, 89%). R_f = 0.63 (5:1 hexanes:ethyl acetate).

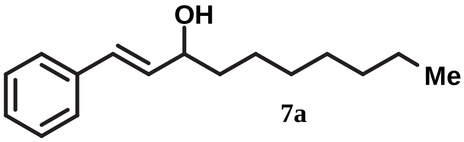
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.46 (s, 1H), 7.32 – 7.17 (m, 5H), 4.40 (ddd, J = 7.5, 7.2, 1.5), 1.75 –1.48 (m, 3H), 1.31 (m, 10H), 0.90 (t, J = 6.9, 3H), –0.02 (s, 9H).

^{13}C NMR (75.40 MHz, CDCl$_3$) δ 147.53, 140.41, 140.27, 128.72, 127.99, 127.11, 76.12, 38.16, 32.07, 29.82, 29.55, 26.27, 22.89, 14.33, 1.07.

IR (film, CH$_2$Cl$_2$): 3362, 2954, 2927, 1593, 1466, 1249, 876 cm^{-1}.

LRMS (EI) m/e calcd (M$^+$): 304, found 304.

The assignment of olefin geometry was based on comparison of the ^{1}H NMR data with those of similar compounds,[2] with the diagnostic evidence being the chemical shift of the alkene proton.



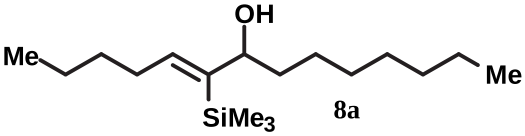
7a

***(E)*-1-phenyl-1-decen-3-ol (7a**, Table 2, entry 5). In the reductive coupling of phenylacetylene (**1c**, 2.0 mmol, 0.22 mL) and octanal (**2c**, 1.0 mmol, 0.16 mL), the standard procedure was used, except that 200 mol% phenylacetylene was used. Silica gel chromatography afforded **7a** as a colorless oil (114 mg, 49%). R_f = 0.50 (5:1 hexanes:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.32 – 7.13 (m, 5H), 6.48 (d, *J* = 15.9, 1H), 6.14 (dd, *J* = 15.9, 6.6, 1H), 4.19 (dt, *J* = 6.6, 6.3, 1H), 1.67 (br s, 1H), 1.55 (dt, *J* = 6.3, 6.9, 2H), 1.20 (br m, 10H), 0.80 (t, *J* = 6.9, 3H).

^{13}C NMR (75.40 MHz, CDCl$_3$) δ 136.99, 132.80, 130.47, 128.80, 127.84, 126.69, 73.40, 37.59, 32.07, 29.80, 29.51, 25.71, 22.90, 14.35.

Spectral data were identical with those previously reported.[3]



8a

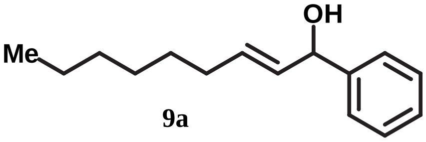
***(Z)*-6-(trimethylsilyl)-5-tetradecen-7-ol (8a**, Table 2, entry 6). In the reductive coupling of 1-trimethylsilyl-1-hexyne (**1b**, 2.0 mmol, 0.40 mL) and octanal (**2c**, 2.0 mmol, 0.30 mL), the standard procedure was used with the exception that the scale was doubled. Silica gel chromatography (19:1 hexanes:ethyl acetate) afforded **8a** as a colorless oil (327 mg, 58%). R_f = 0.53 in 9:1 hexanes:ethyl acetate.

^{1}H NMR (300 MHz, CDCl$_3$): δ 6.19 (dt, *J* = 1.1, 7.4 Hz, 1H), 4.14 (t, *J* = 6.0 Hz, 1H), 2.14 (m, 2H), 1.37 (m, 17H), 0.90 (m, 6H), 0.18 (s, 9H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 142.57, 142.08, 77.10, 38.17, 32.42, 32.10, 31.71, 29.85, 29.59, 26.50, 22.95, 22.77, 14.41, 14.37, 1.10.

IR (thin film NaCl): 3450, 2928, 1611, 1458, 1320, 1248, 836, 759 cm^{-1}.

LRMS (CI) m/e calcd (M$^+$): 284, found 285 [(M+H)$^+$].



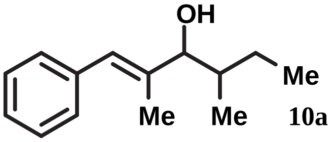
9a

***(E)*-1-phenyl-2-nonen-1-ol (9a**, Table 2, entry 7). In the reductive coupling of 1-octyne (**1e**, 2.0 mmol, 0.30 mL) and benzaldehyde (**2a**, 1.0 mmol, 0.10 mmol), the standard procedure was used, except that 200 mol% 1-octyne was used. Silica gel chromatography afforded **9a** as a colorless oil (167 mg, 76%). R_f = 0.51 (5:1 hexanes:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31 – 7.18 (m, 5H), 5.68 (dt, *J* = 15.3, 6.3, 1H), 5.58 (ddt, *J* = 15.5, 6.3, 1.2, 1H), 5.08 (d, *J* = 6.0, 1H), 1.98 (dt, *J* = 6.6, 6.9, 2H), 1.84 (br s, 1H), 1.33 – 1.12 (m, 8H), 0.80 (t, *J* = 6.9, 3H).

^{13}C NMR (75.40 MHz, $CDCl_3$) δ 143.59, 133.01, 132.38, 128.61, 127.62, 126.33, 75.38, 32.38, 31.86, 29.21, 29.06, 22.79, 14.27.

Spectral data were identical with those previously reported.[4]



10a

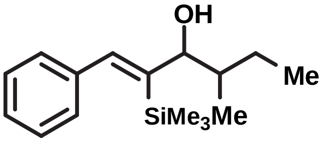
***(E)*-2,4-dimethyl-1-phenyl-1-hexen-3-ol (10a**, Table 2, entry 8). In the reductive coupling of 1-phenylpropyne (**1a**, 2.0 mmol, 0.26 mmol) and 2-methylbutyraldehyde (**2d**, 2.0 mmol, 0.22 mL), the general procedure was used with the exception that the reaction was conducted at 110 °C and that the scale was doubled. Silica gel chromatography (9:1 hexanes:ethyl acetate) afforded **10a** as a pale yellowish oil (167 mg, 41%). Diastereomeric ratio = 66:34. R_f = 0.50 in 4:1 hexanes:ethyl acetate.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.39 (m, 5H), 6.49 (s, 1H, major), 6.45 (s, 1H, minor), 3.96 (d, *J* = 6.6 Hz, 1H, major), 3.87 (d, *J* = 8.2, 1H, minor), 0.76-2.28 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.78, 137.77, 137.65, 129.08, 127.21, 126.53, 126.45, 126.29, 83.09, 81.74, 37.94, 26.55, 25.04, 15.90, 14.35, 14.20, 13.36, 11.97, 11.54.

IR (thin film, NaCl): 3405, 2926, 1599, 1448, 1379, 1007, 749, 699 cm^{-1}.

HRMS (EI) m/e calcd (M+): 204.1513, found 204.1506.



11a

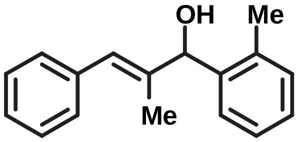
***(Z)*-4-methyl-1-phenyl-2-(trimethylsilyl)-1-hexen-3-ol (11a**, Table 2, entry 9). In the reductive coupling of 1-phenyl-2-(trimethylsilyl)-acetylene (**1b**, 2.0 mmol, 0.40 mL) and 2-methylbutyraldehyde (**2d**, 2.0 mmol, 0.22 mL), the general procedure was used with the exception that the scale was doubled. Silica gel chromatography (19:1 hexanes:ethyl acetate) afforded **11a** as a pale yellowish oil (162 mg, 31%). Diastereomeric ratio = 58:42. R_f = 0.41 in 9:1 hexanes:ethyl acetate.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.7 Hz, 1H), 7.17 (m, 5H), 4.31 (broad s, 1H, major), 4.11 (d, *J* = 4.7 Hz, 1H), 1.58 (m, 3H), 1.28 (m, 1H), 0.91 (m, 8H), -0.12 (s, 9H, minor), -0.13 (s, 9H, major).

^{13}C NMR (75 MHz, $CDCl_3$): δ 146.22, 146.00, 141.29, 140.51, 140.30, 128.59, 128.58, 127.87, 127.01, 126.95, 80.91, 77.57, 76.81, 39.62, 39.33, 27.67, 22.75, 17.10, 12.51, 12.37, 12.03, 1.24, 1.05.

IR (thin film, NaCl): 3395, 2961, 1593, 1491, 1461, 1248, 1134, 1029, 838, 735, 698 cm^{-1}.

HRMS (EI) m/e calcd (M+): 262.175294, found 262.1748



12a

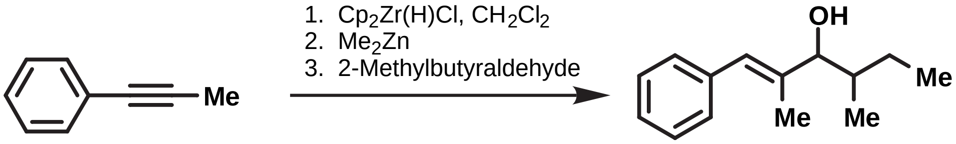
***(E)*-2-methyl-1-(2'-methylphenyl)-3-phenyl-2-propen-1-ol (12a**, Table 2, entry 10). In the reductive coupling of 1-phenylpropyne (**1a**, 2.0 mmol, 0.26 mL) and *o*-tolualdehyde (**2e**, 2.0 mmol, 0.23 mL), the general procedure was used with the exception that the scale was doubled. Silica gel chromatography (9:1 hexanes:ethyl acetate), afforded **12a** as a white solid (391 mg, 83 %), m.p. 83-85 °C. R_f = 0.58 (4:1 hexanes:ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 2.1 Hz, 1H), 7.35-7.19 (m, 8H), 6.73 (s, 1H), 5.77 (q, 1H, *J* = 6.9 Hz, minor regioisomer), 5.46 (d, *J* = 3.1 Hz, 1H), 2.40 (s, 3H), 2.26 (s, 3H, minor regioisomer), 1.97 (s, 3H, minor regioisomer), 1.77 (d, *J*=1.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.87, 140.09, 139.86, 138.59, 137.83, 135.33, 130.51, 130.10, 129.01, 128.14, 128.03, 127.51, 127.21, 126.86, 126.50, 126.44, 126.35, 126.10, 125.87, 124.03, 76.04, 74.83, 19.57, 19.41, 14,82, 14.66.

IR (thin film, NaCl): 3333, 3053, 3022, 2915, 1599, 1488, 1442 cm^{-1}.

HRMS (EI) m/e calcd (M+): 238.135765, found 238.1363.



1a **10a**

***(E)*-2,4-dimethyl-1-phenyl-1-hexen-3-ol (10a**, ref. 15). To a Schlenck flask under Ar atmostphere were added 1-phenylpropyne (0.28 mL, 2.2 mmol) and 7 mL dichloromethane. Bis(cyclopentadienyl)zirconium chloride hydride (0.567 g, 2.2 mmol) was then added under a positive flow of argon. When the solution became homogeneous, the reaction mixture was cooled to – 61 °C (chloroform/dry ice), and diethyl zinc (2.2 mL of a 1.0M solution in hexanes, 2.2 mmol) was added dropwise via syringe. Upon warming to 0 °C, 2-methylbutyraldehyde (0.21 mL, 2.0 mmol) was added and stirring continued 1.5 h at 0 °C before stirring at ambient room temperature 6 h. A saturated solution of NH_4Cl (25 mL) was added, and the mixture was extracted with ether (3 x 60 mL). Concentration *in vacuo* and silica gel chromatography afforded **10a** as a yellow oil (160 mg, 39%). R_f = 0.53 in 9:1 hexanes:ethyl acetate. R_f = 0.50 in 4:1 hexanes:ethyl acetate.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.39 (m, 5H), 6.49 (s, 1H, major), 6.45 (s, 1H, minor), 5.78 (m, 1H, regioisomers), 3.96 (d, *J* = 6.6 Hz, 1H, major), 3.87 (d, *J* = 8.2, 1H, minor), 0.76-2.28 (m, 12H).

Preliminary Mechanistic Investigations (cf. Scheme 1):

(a) Omission of aldehyde (cf. Table 2, entry 4): Treatment of alkyne **1b** (0.25 mmol) with Et_3B (0.50 mmol), $Ni(COD)_2$ (0.25 mmol), and Bu_3P (0.50 mmol) for 16 h in toluene followed by treatment of the reaction with aqueous HCl provided recovered alkyne (86%) and no trace of allylic alcohol **6a** or products of reduction or oligomerization.

In a parallel experiment, treatment of an equivalent reaction mixture after 16 h with additional portions of Et_3B (4.5 mmol) and alkyne **1b** (2.5 mmol), along with aldehyde **2c** (2.25 mmol), afforded a 77% yield of allylic alcohol **6a**.

From these experiments it was concluded that an irreversible hydrometallation of the alkyne does not occur under the reaction conditions, unless this process is dependent on the presence of aldehyde.

(b) Omission of Et_3B (cf. Table 2, entry 4): A solution of $Ni(COD)_2$ (0.25 mmol), Bu_3P (0.50 mmol), alkyne **1b** (2.5 mmol), and aldehyde **2c** (2.25 mmol) in toluene was stirred 16 h at ambient temperature. Treatment of the reaction mixture with aqueous HCl provided recovered alkyne **1b** (92%) and no trace of allylic alcohol **6a** or products of reduction or oligomerization of the alkyne.

In a parallel experiment, treatment an equivalent reaction mixture after 16 h with additional portions of alkyne **1b** (2.5 mmol) and aldehyde **2c** (2.25 mmol), along with Et_3B (5.0 mmol), afforded an 81% yield of allylic alcohol **6a**.

From these results it was concluded that the reaction does not proceed via intermediate **B**, unless Et_3B is required for its formation.

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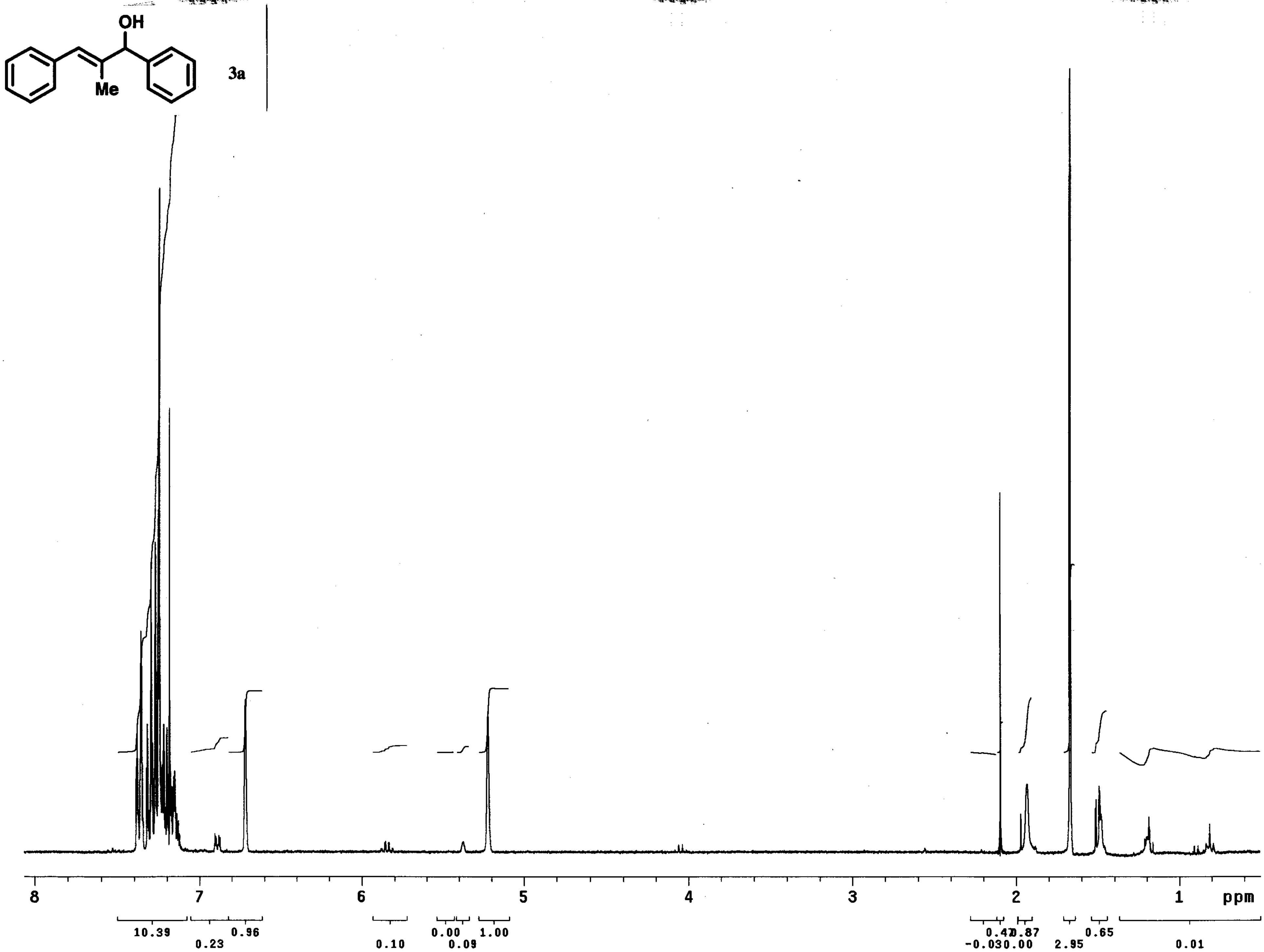
[1] Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, 54, 2411.

[2] Mitchell, T. N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, 52, 4868. (b) Chatani, N.; Takeyashu, T.; Hanafusa, T. *Tetrahedron Lett.* **1986**, 27, 1841. (c) Shipman M.; Thorpe, H. R.; Clemens, I. R. *Tetrahedron* **1998**, 54, 14265.

[3] Chandrasekhar S.; Takhi, M.; Yadar, J.S. *Tetrahedron Lett.* **1995**, 36, 307.

[4] Maier, M. E.; Oost, T. *J. Organomet. Chem.* **1995**, 505, 95.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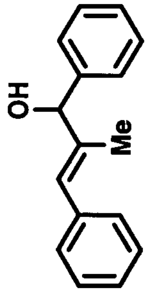
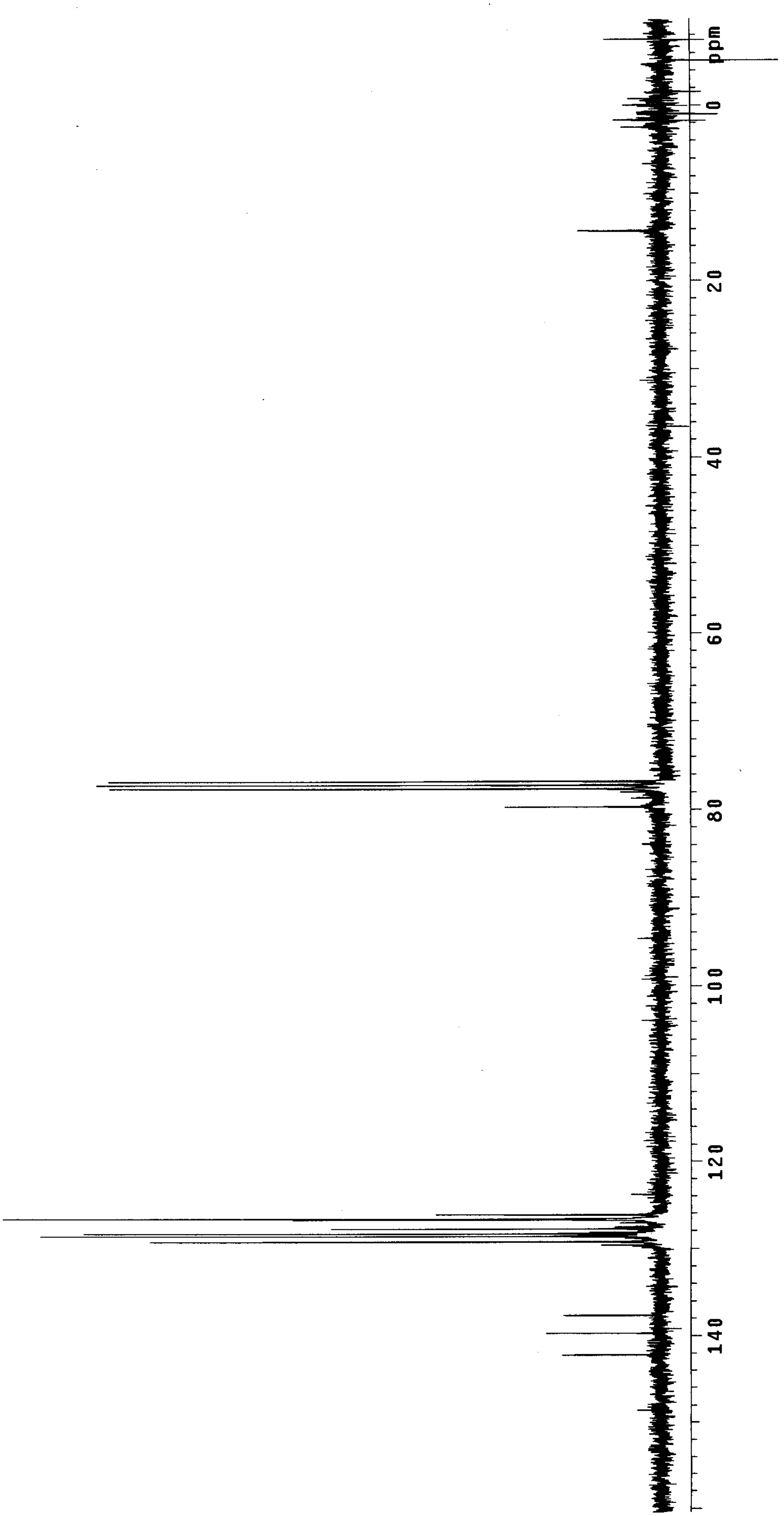
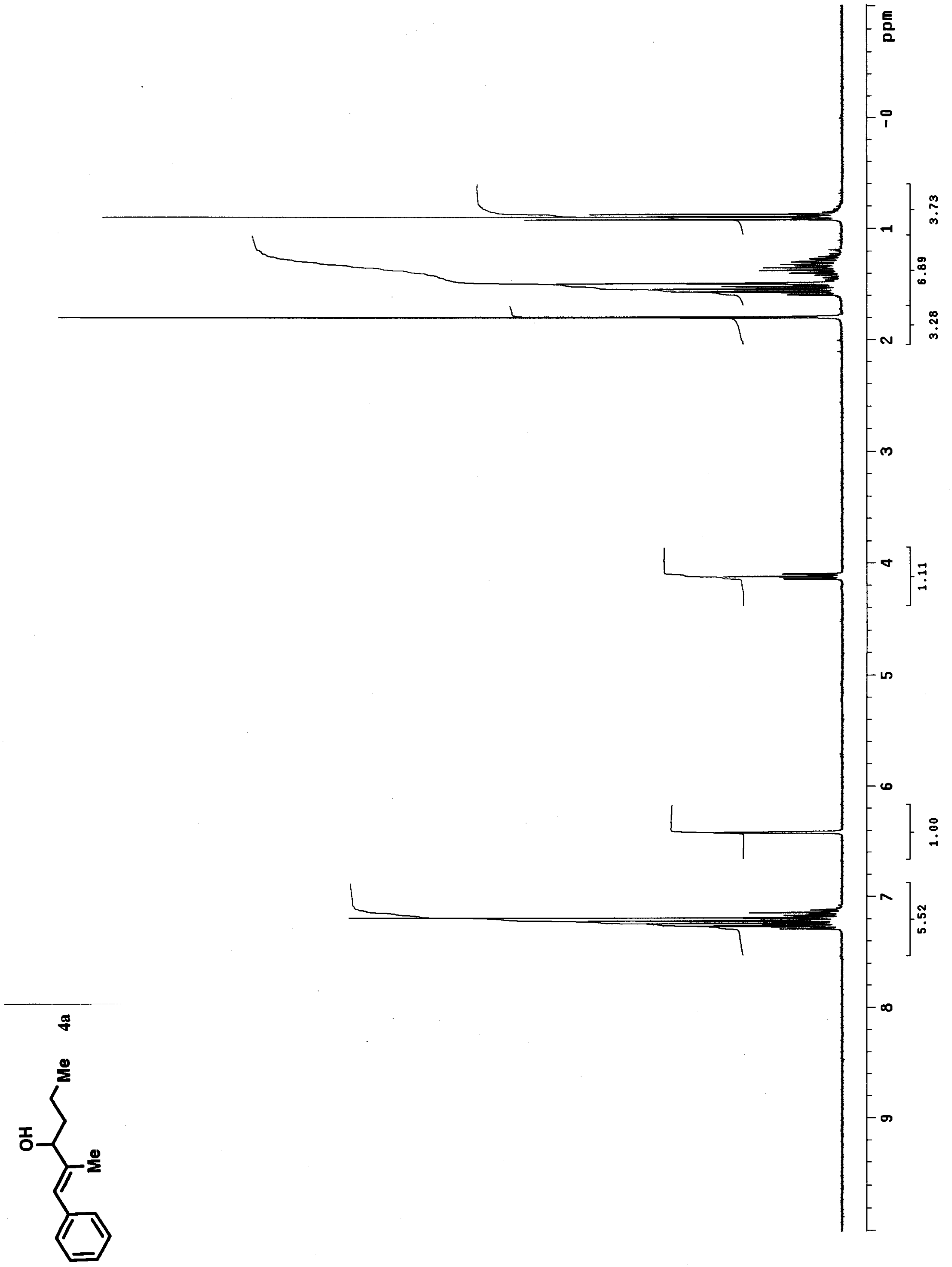


3a




4a

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 Ambient temperature
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OBSERVE  C13,  75.4003864 MHz
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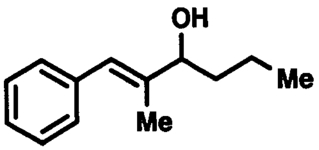
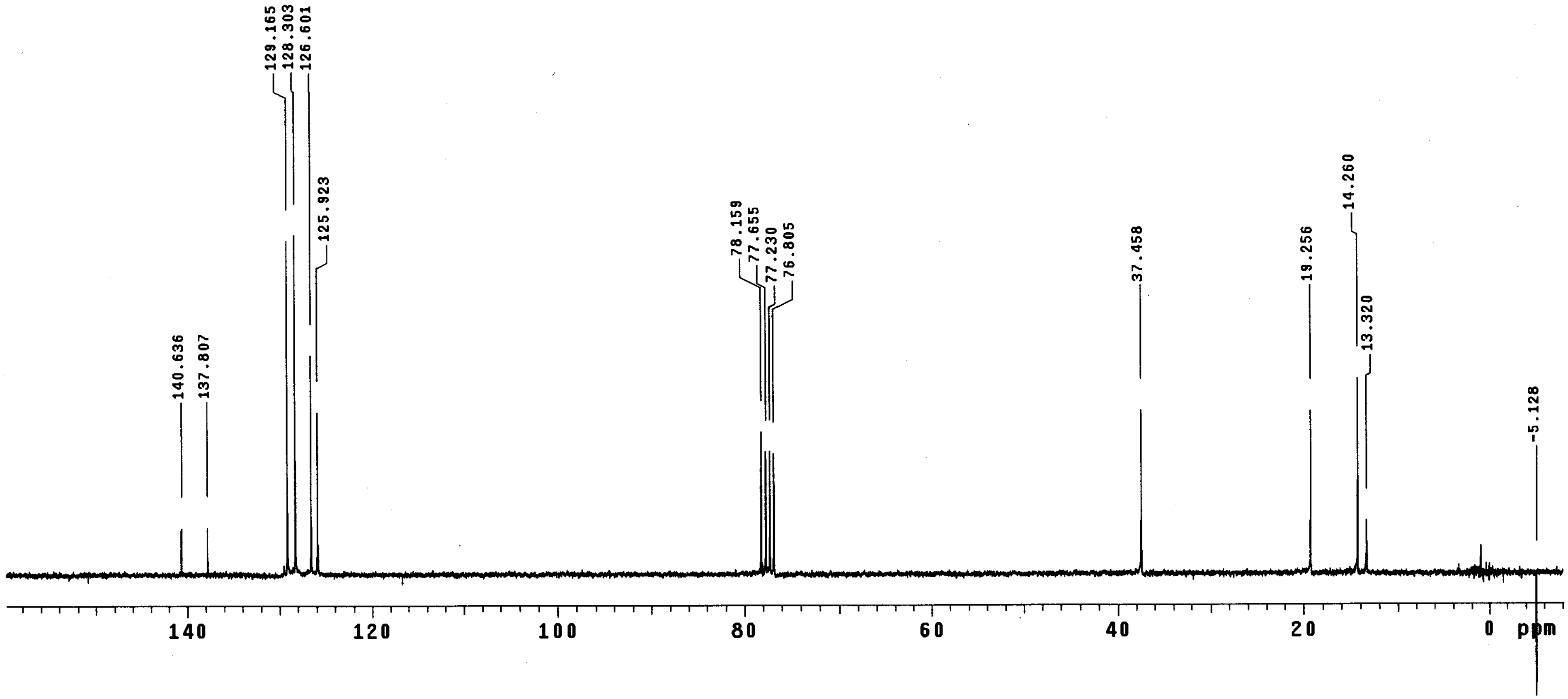
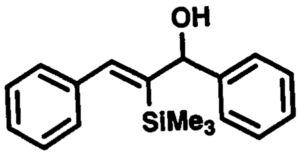
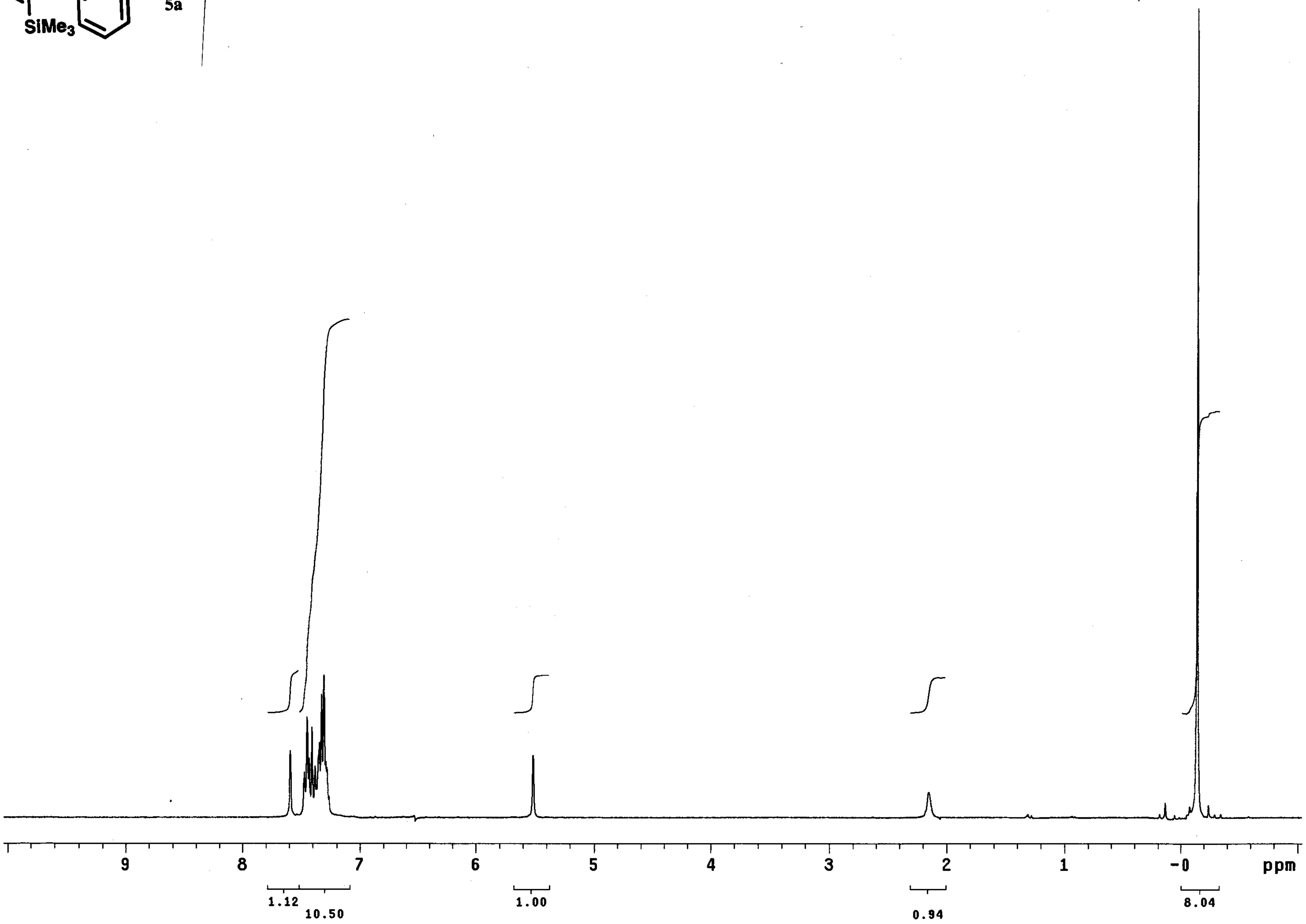


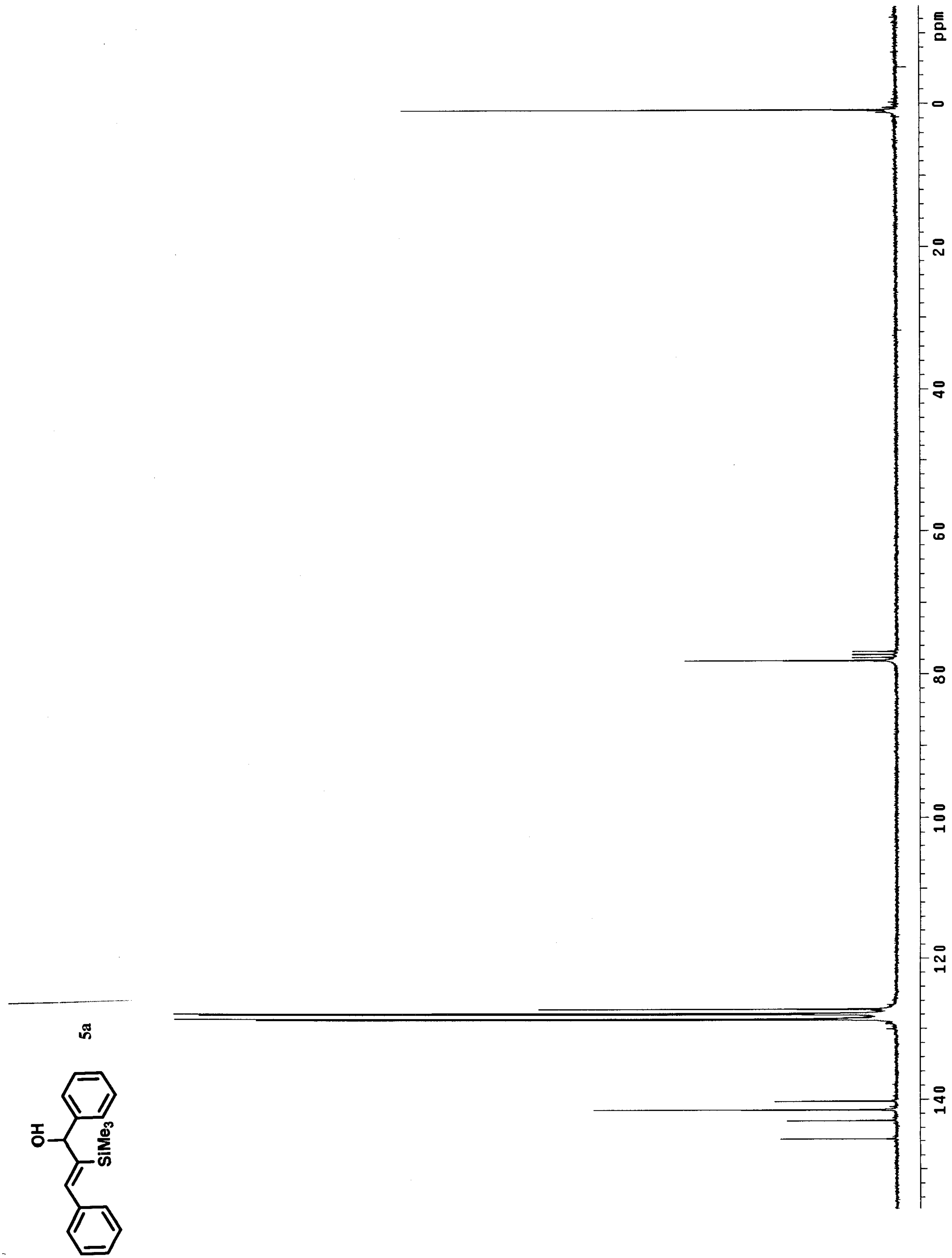
4a





5a





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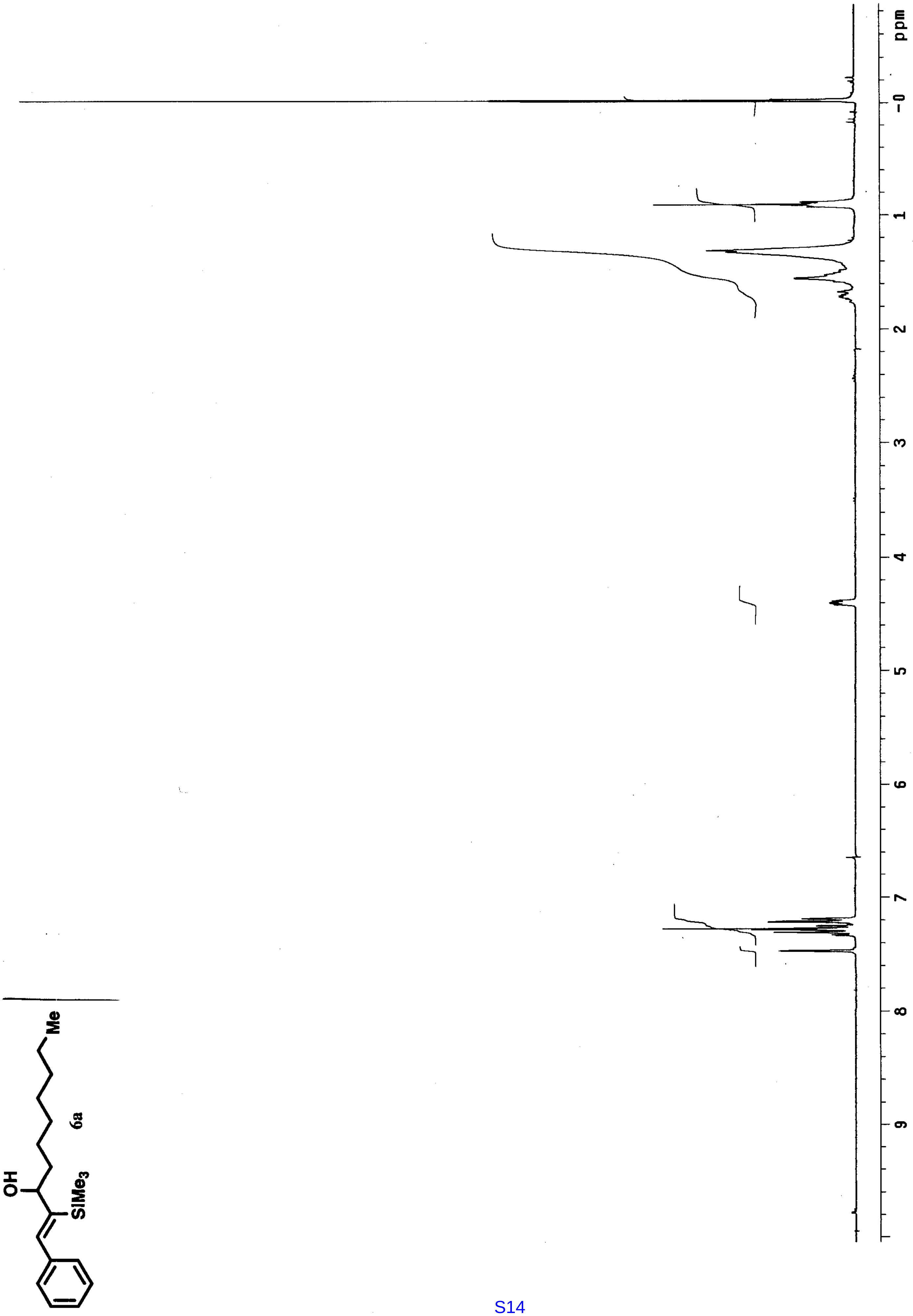

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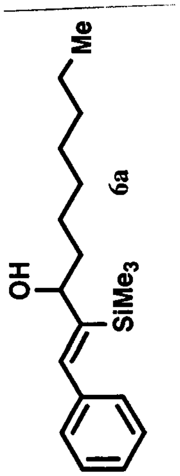

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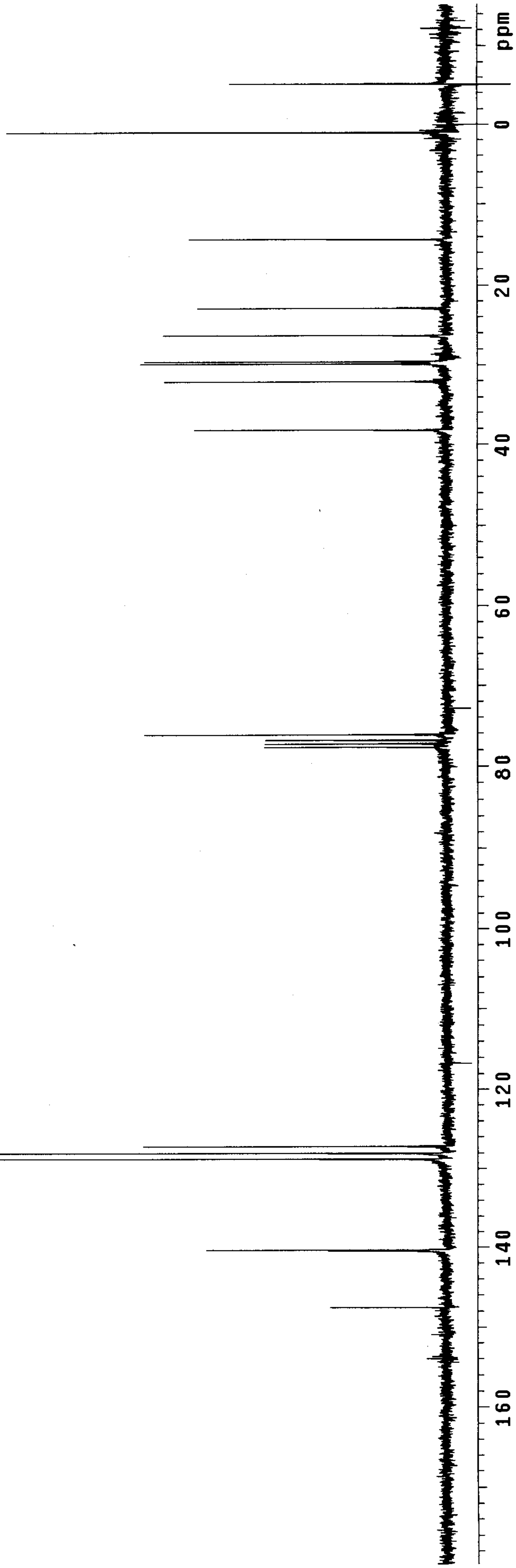

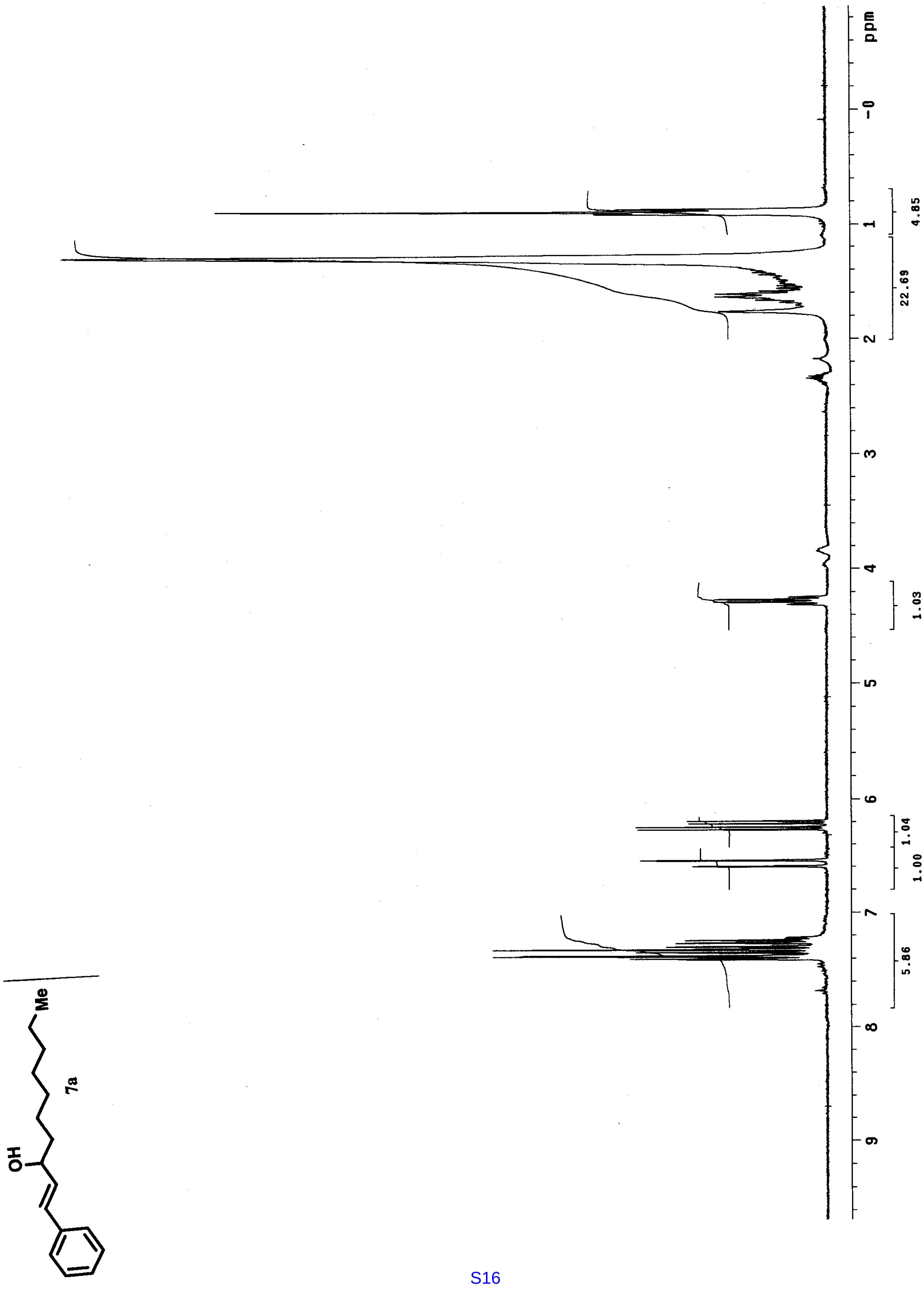

OH
Me
7a
ppm
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1
2
3
4
5
6
7
8
9
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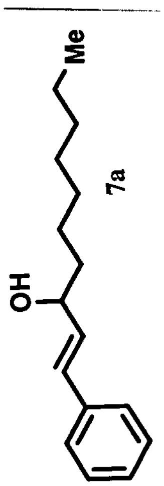
22.69
1.03
1.04
1.00
5.86



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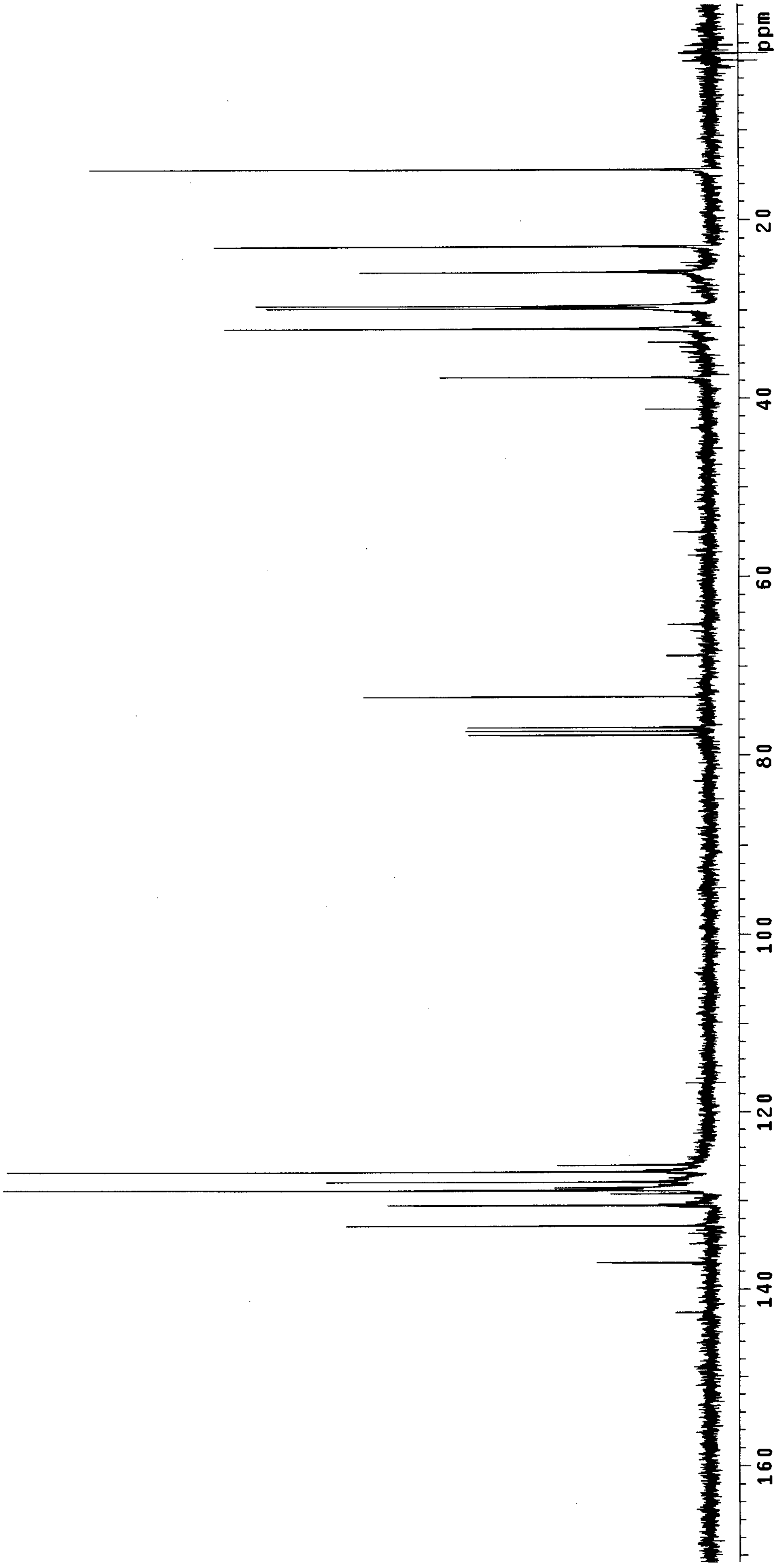
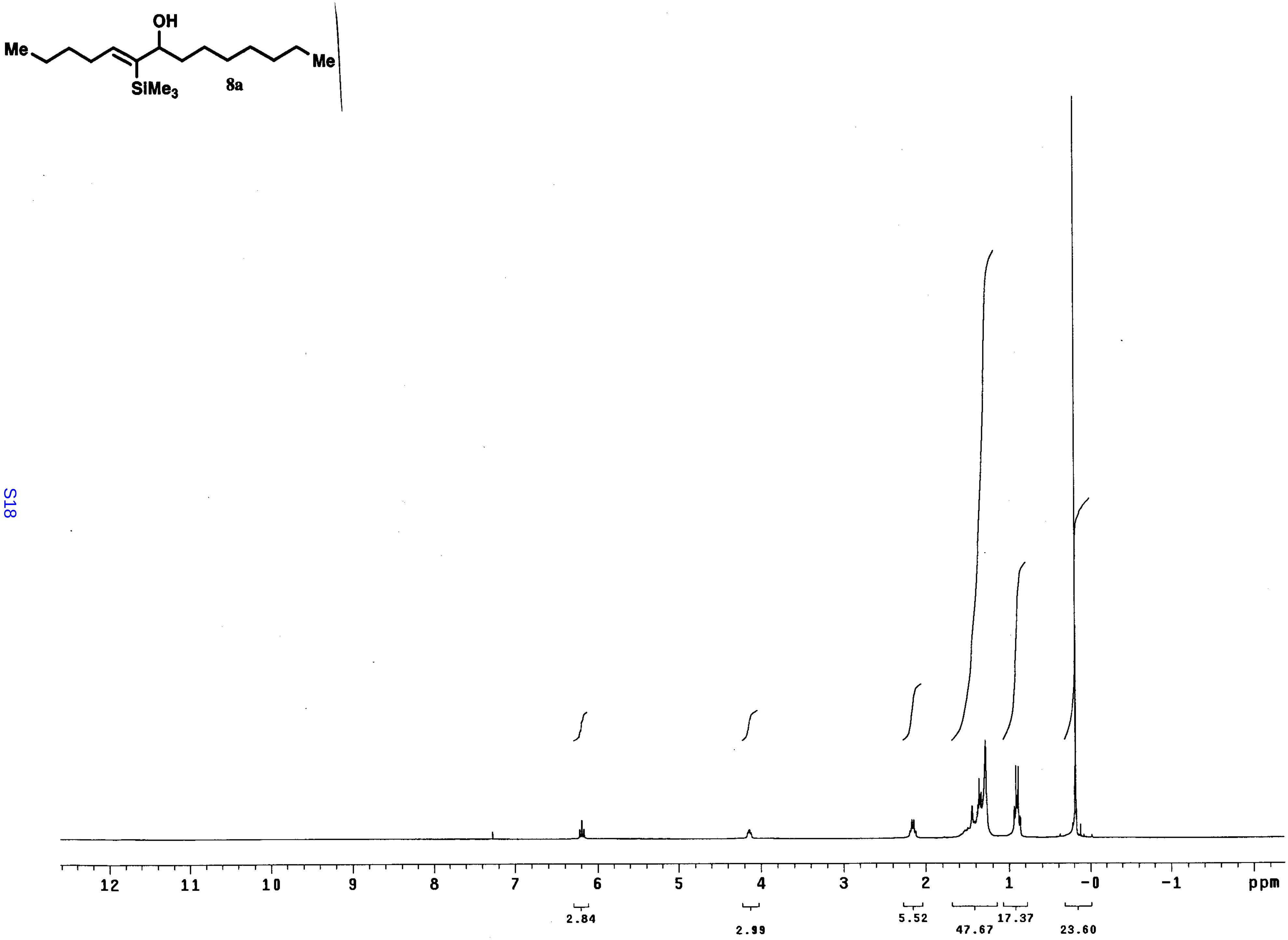
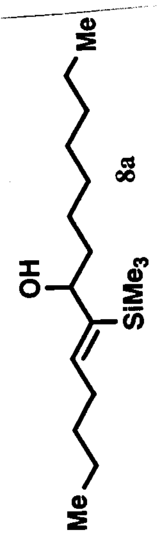
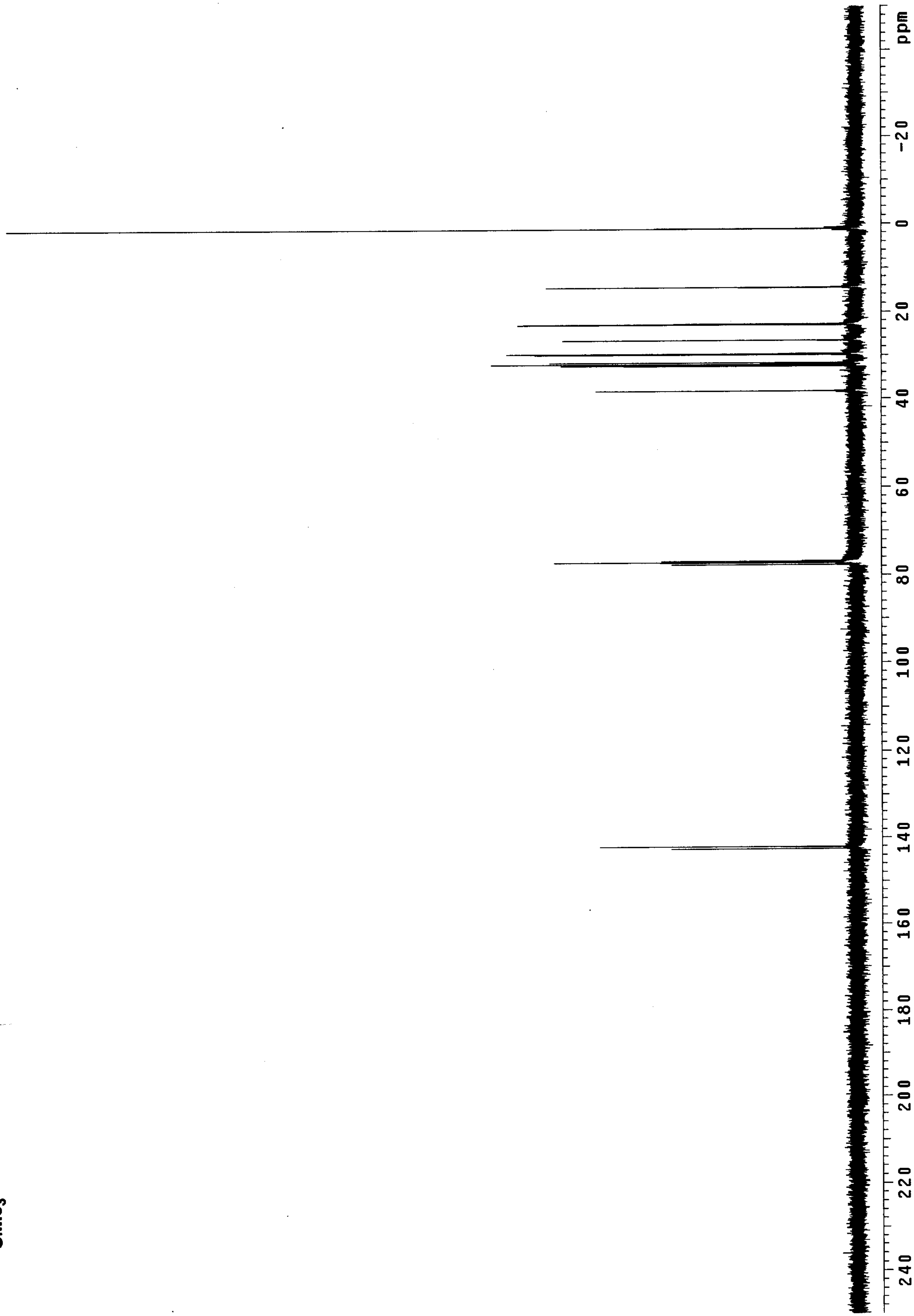


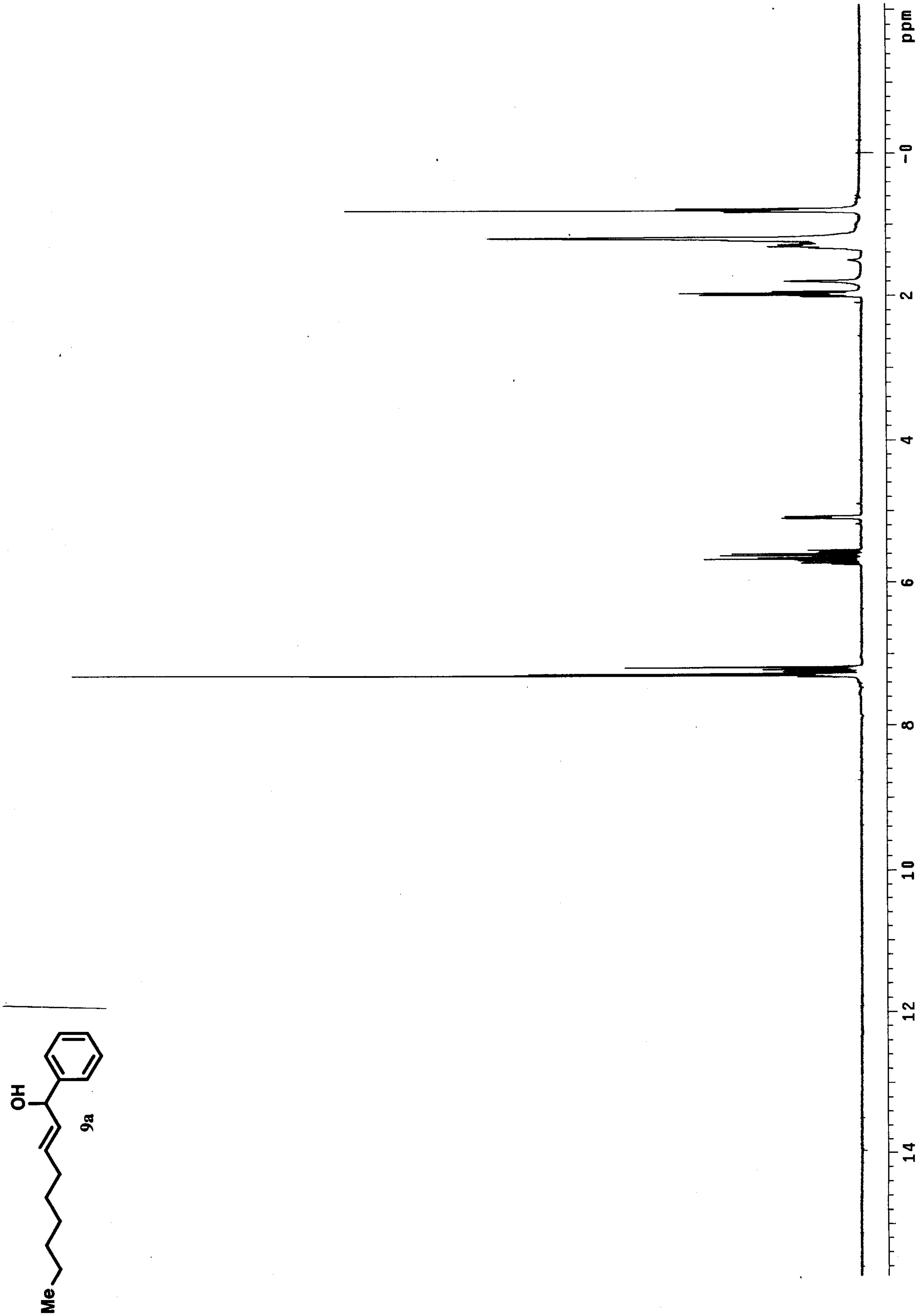


OH
Me
SiMe$_3$
8a
Me
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
2.84
2.99
5.52
47.67
17.37
23.60



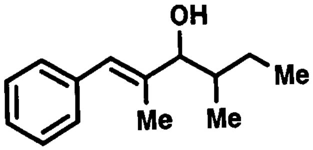
8a



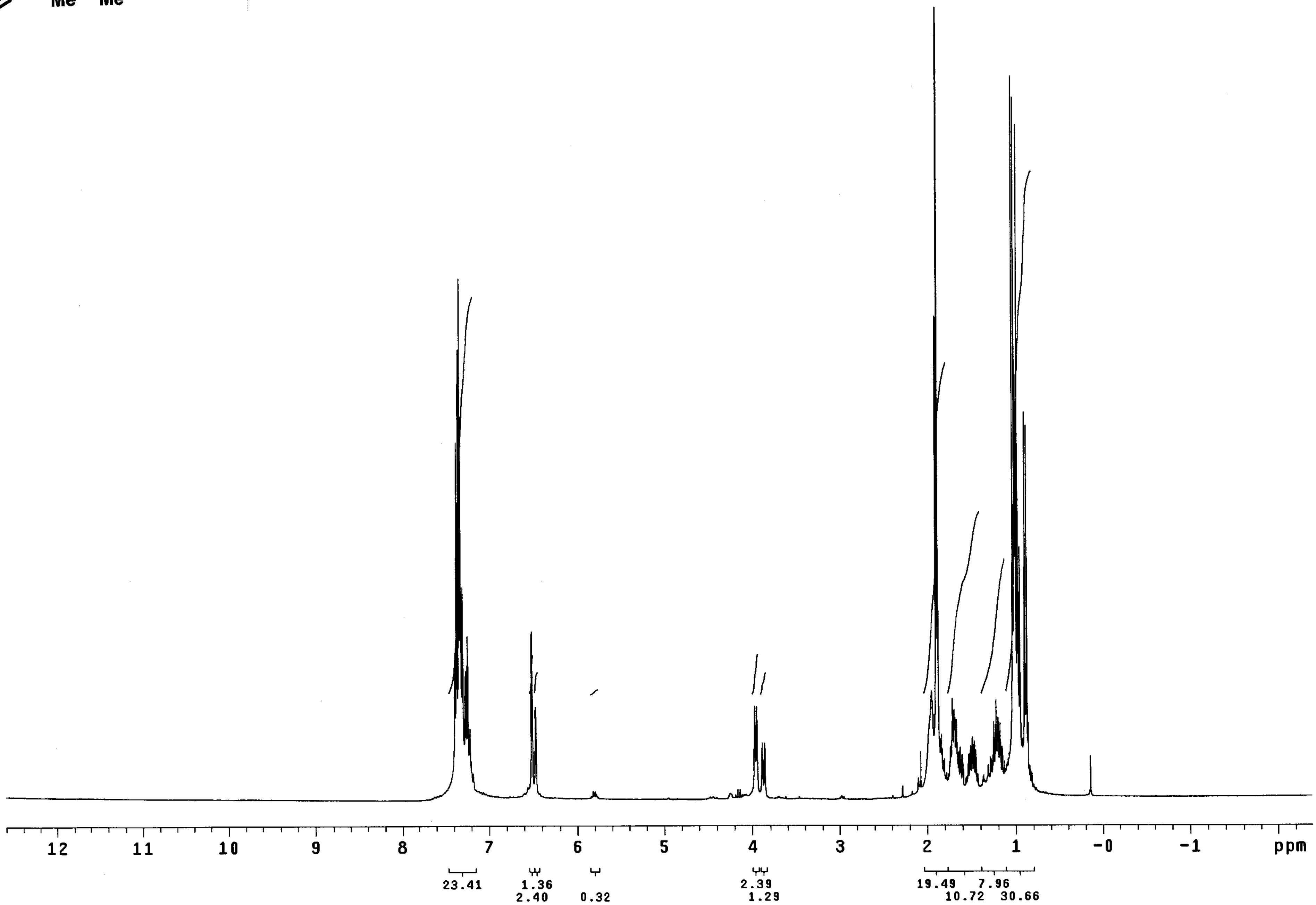


9a

9a



10a


12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
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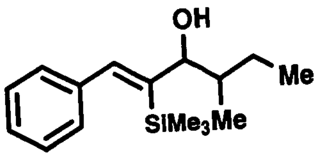
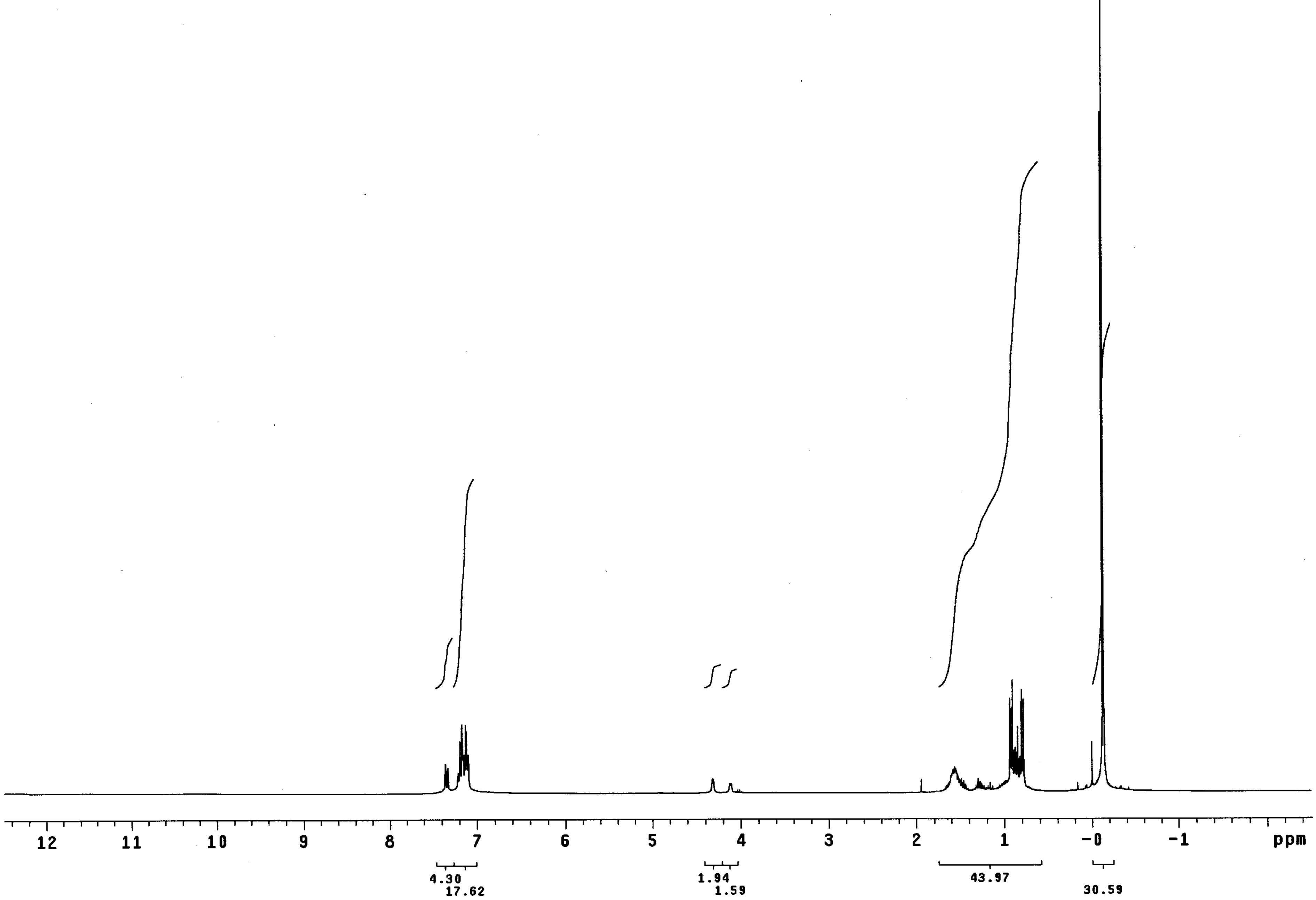
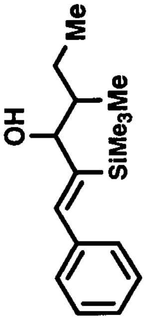
1.36
2.40
0.32
2.39
1.29
19.49
10.72
7.96
30.66

10a



11a





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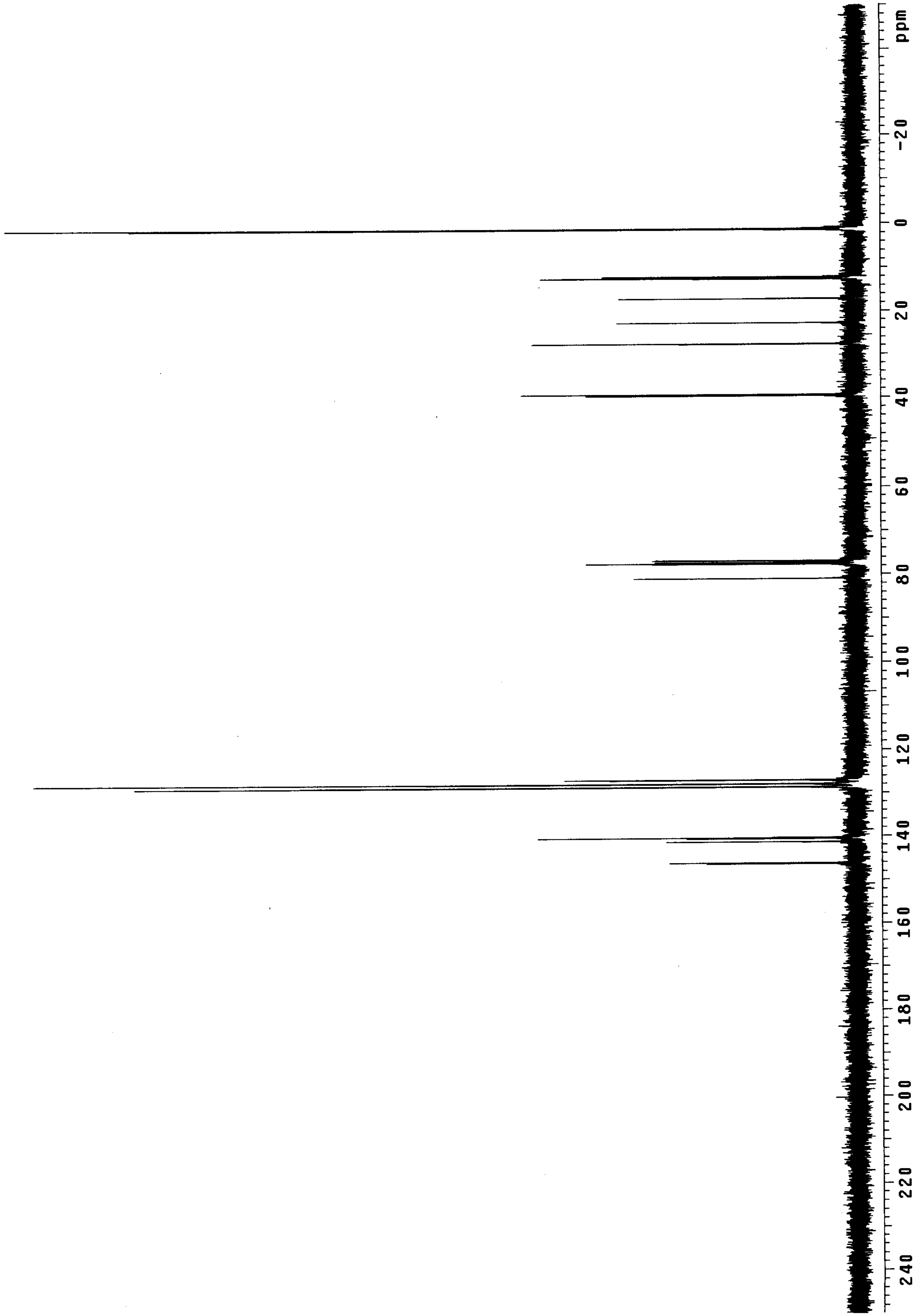

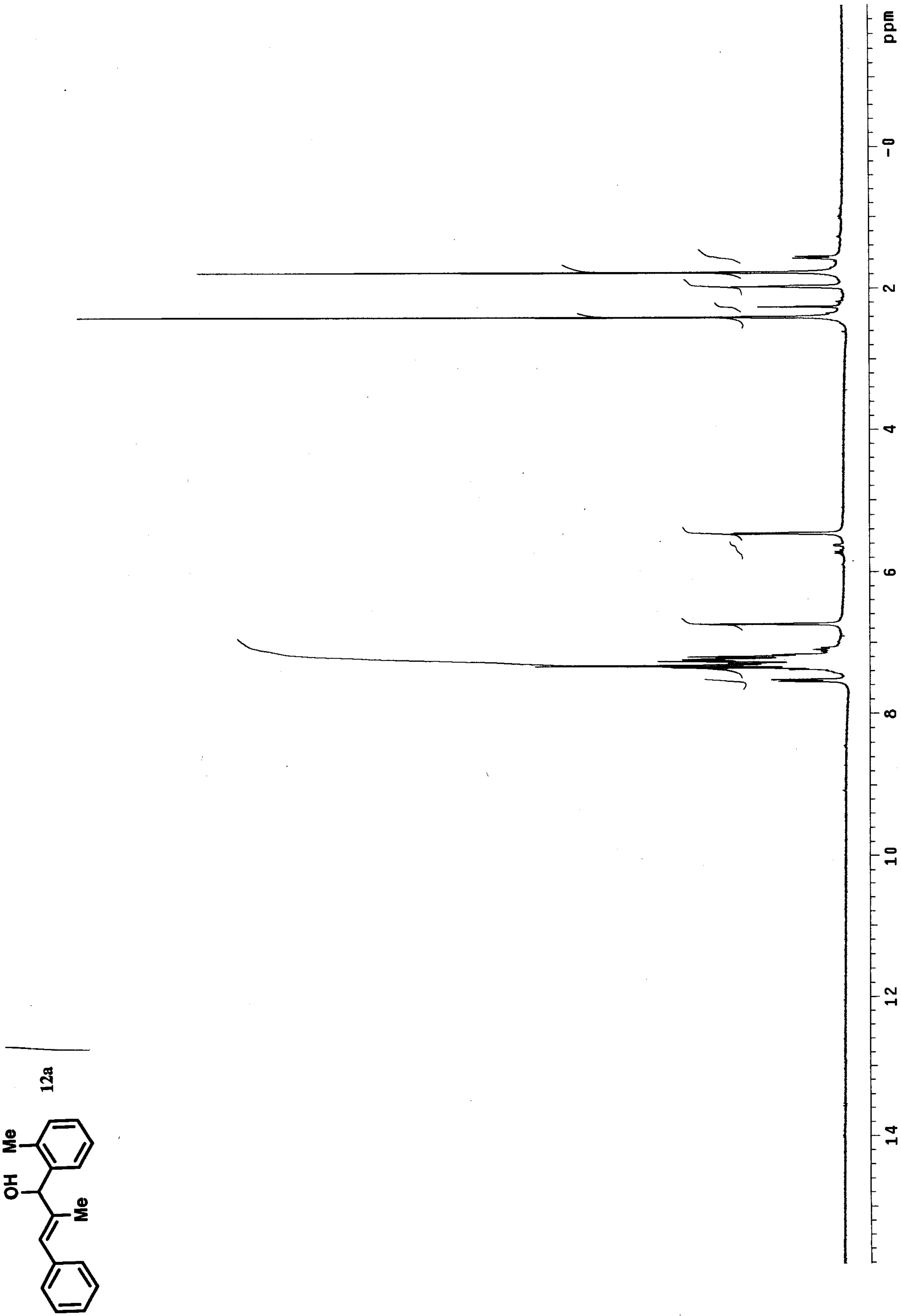
OH
Me
Me
ppm
14
12
10
8
6
4
2
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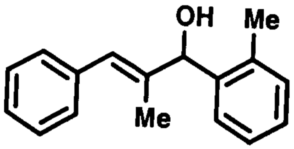
43.94
5.30
1.10
5.21
14.39
2.37
5.03
3.75
15.63

12a



12a