Catalytic Asymmetric Reductive Coupling of Alkynes and Aldehydes: Enantioselective Synthesis of Allylic Alcohols and α-Hydroxy Ketones

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Supporting Information

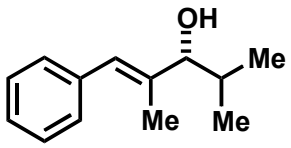
Experimental

General Methods. $Ni(cod)_2$ and (S)-(+)-neomenthyldiphenylphosphine (NMDPP) were purchased from Strem Chemicals, Inc. and used without further purification. Triethylborane (98%) was purchased from Aldrich Chemical Co. Solutions of triethylborane were prepared by adding neat Et_3B to the appropriate freshly-distilled, thoroughly-degassed solvent. 1-phenyl-1-propyne, 1-phenyl-1-butyne, 1-phenyl-1-pentyne, 1-phenyl-2-(trimethylsilyl)acetylene, 4-octyne, and all aldehydes were purchased from Aldrich Chemical Co. or Alfa Aesar. All aldehydes were distilled prior to use. Methylene chloride and DMI were distilled over calcium hydride; ethyl acetate was distilled over magnesium sulfate under argon atmosphere.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates precoated with a fluorescent indicator. The developed plates were analyzed with UV light and stained with 12-molybdophosphoric acid (PMA) stain. Flash chromatography was performed using silica gel 60 (40-63 μm) from Silicycle. NMR spectra were recorded on 300 and 500MHz Varian instruments. IR spectra were recorded as a thin film between NaCl plates on a Perkin-Elmer Model 2000 FTIR instrument. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD, AD, or OJ column. GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Temperatures were maintained using a Thermo Neslab CC-65 cryocool immersion cooler equipped with Cryotrol temperature controller.

Standard Experimental Procedure for Asymmetric Catalytic Reductive Coupling of Alkynes and Aldehydes

In a glovebox, $Ni(cod)_2$ (14 mg, 0.5 mmol), and (+)-NMDPP (32 mg, 0.1 mmol) were placed into a 50 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and Et_3B (2.0 M in ethyl acetate, 0.5 mL, 1 mmol) and DMI (0.5 mL) were added via syringe. The resulting solution was stirred at ambient temperature for 10 minutes and then placed in an isopropanol bath which had been precooled to −25 °C. The solution was stirred at this temperature for 15 minutes, and then the alkyne (0.5 mmol) was added. The aldehyde (1.0 mmol) was then added over 8 h either in bursts or dropwise via syringe pump (the two modes of addition are functionally equivalent). The reaction was stirred at −25 °C for an additional 36 h, at which point saturated aqueous NH_4Cl (3 mL) and 1M HCl (0.5 mL) were added. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL), and the organic layer was extracted (3 x 20 mL), dried and condensed. The crude mixture was then purified by silica gel chromatography using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). An additional column (toluene: EtOAc; 10:1) was sometimes necessary to completely remove aldol dimer, which is a common reaction byproduct.



(*E*)-2,4-Dimethyl-1-phenyl-pent-1-en-3-ol (**1**).

In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 63 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at -25 °C, the standard procedure was used with burst addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded **1** as a clear oil (91 mg, 95% yield, 90% ee, >95:5 regioselectivity). R_f = 0.22 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 -7.37 (m, 5H), 6.48 (s, 1H), 3.80 (d, *J* = 8, 1H), 1.87-1.93 (m, 1H), 1.87 (s, 3H), 1.05 (d, *J* = 6.5, 3H), 0.91 (d, *J* = 6.5, 3H).

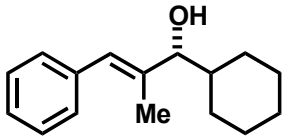
^{13}C NMR (500 MHz, $CDCl_3$) δ 139.86, 137.79, 129.19, 128.31, 127.06, 126.62, 84.34, 31.58, 19.75, 18.59, 13.45.

IR (thin film NaCl): 3396, 3057, 3024, 2958, 2871, 1600, 1491, 1447, 1382, 1295.

HRMS (ESI) *m/z* 213.125 [$(M + Na)^+$; calcd for $C_{13}H_{18}O$: 213.125].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1**] = 13.8 min; t_R[(*S*)-**1**] = 15.6 min.

$[\alpha]_D$ = –47.27 (25 ºC, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(*E*)-1-Cyclohexyl-2-methyl-3-phenyl-prop-2-en-1-ol (**2**).

In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 63 μL) and cyclohexanecarboxaldehyde (112 mg, 1.0 mmol, 121 μL) at -25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded **2** as a clear oil (125 mg, 97% yield, 90% ee, >95:5 regioselectivity). R_f = 0.25 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.36 (m, 5H); 6.44 (s, 1H); 3.84 (d, *J* = 8, 1H); 2.04 − 2.08 (m, 1H); 1.87 (s, 3H); 1.67 – 1.83 (m, 4H); 1.54 – 1.59 (m, 2H); 1.17 – 1.30 (m, 2H); 0.98 – 1.06 (m, 2H).

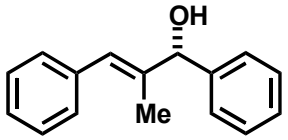
^{13}C NMR (500 MHz, $CDCl_3$) δ 139.58, 137.74, 129.17, 128.29, 127.25, 126.59, 83.47, 41.08, 29.91, 29.24, 26.65, 26.38, 26.20, 13.33.

IR (thin film NaCl): 3395, 3081, 3056, 3023, 2934, 2852, 1944, 1722, 1599, 1575, 1494, 1449.

HRMS (EI) *m/z* 230.167 [M^+; calcd for $C_{16}H_{22}O$: 230.167].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98.5:1.5, 0.5 mL/min): t_R[(*R*)-**2**] = 36.5 min; t_R[(*S*)-**2**] = 40.6 min.

$[\alpha]_D$ = –19.05 (25 ºC, 589 nm, 1.05 g/100 mL, $CHCl_3$).



(*E*)-2-Methyl-1,3-diphenyl-prop-2-en-1-ol (**3**).

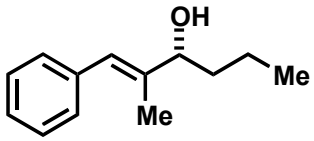
In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 64 μL) and benzaldehyde (106 mg, 1.0 mmol, 102 μL) at -25 °C, the standard procedure was used with burst addition of the aldehyde over 8 h. Silica gel chromatography afforded **3** as a clear oil (88 mg, 79% yield, 73% ee, 91:9 regioselectivity). R_f = 0.41 (5:1 hexanes: ethyl acetate). Spectral data were identical to those previously reported.[1]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 10H); 6.72 (s, 1H); 5.22 (s, 1H); 1.94 (bs, 1H); 1.67 (d, *J* = 1.5, 3H).

^{13}C NMR (500 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.

Chiral HPLC analysis (Chiralcel AD, hexanes: 2-propanol, 99:1, 0.5 mL/min): t_R[(*R*)-**3**] = 70.7 min; t_R[(*S*)-**3**] = 66.2 min.

$[\alpha]_D$ = –2.48 (25 ºC, 589 nm, 1.09 g/100 mL, $CHCl_3$).



(*E*)-2-Methyl-1-phenyl-hex-1-en-3-ol (**4**).

In the reductive coupling of 1-phenyl-1-propyne (58 mg, 0.5 mmol, 64 μL) and butyraldehyde (72 mg, 1.0 mmol, 90 μL) at -10 °C, the standard procedure was used with burst

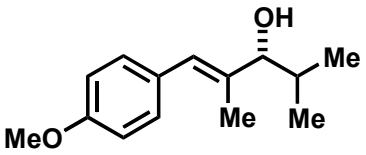
addition of the aldehyde over 6 h (15 μl portions). The reaction was quenched after 10 h. Silica gel chromatography afforded **4** as a clear oil (78 mg, 82% yield, 65% ee, >95:5 regioselectivity). R_f = 0.46 (5:1 hexanes: ethyl acetate). Spectral data were identical to those previously reported.[2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.26 (m, 5H); 6.38 (s, 1H); 4.07 (t, *J* = 6, 1H); 1.88 (bs, 1H); 1.77 (d, *J* = 1, 3H); 1.54 (dt, *J* = 6.9, 7.2, 2H); 1.44 – 1.19 (m, 2H); 0.87 (t, *J* = 7, 3H).

^{13}C NMR (500 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.

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**4**] = 14.8 min; t_R[(*S*)-**4**] = 16.0 min.

$[\alpha]_D$ = –3.37 (25 ºC, 589 nm, 1.01 g/100 mL, $CHCl_3$).



(*E*)-1-(4-Methoxy-phenyl)-2,4-dimethyl-pent-1-en-3-ol (**5**).

In the reductive coupling of 1-methoxy-4-propynyl-benzene[3] (73 mg, 0.5 mmol, 72 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at −25 °C, the standard procedure was used with burst addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded **5** as a clear oil (87 mg, 80% yield, 88% ee, >95:5 regioselectivity). R_f = 0.38 (5:1 hexanes: ethyl acetate). Ozonolysis of **5** (see compound **16** for representative experimental procedure) provided p-anisaldehyde in >90% yield, confirming the structural integrity of the aromatic system.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9, 2H); 6.89 (d, *J* = 9, 2H); 6.40 (s, 1H); 3.82 (s, 3H); 3.77 (d, *J* = 7.5, 1H); 1.87 (sept., *J* = 7, 1H); 1.86 (s, 3H); 1.04 (d, *J* = 7, 3H); 0.88 (d, *J* = 7, 3H).

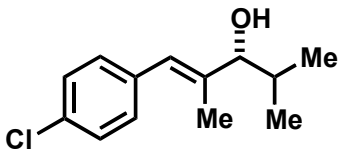
^{13}C NMR (500 MHz, $CDCl_3$) δ 158.28, 138.18, 130.35, 126.61, 113.73, 84.58, 55.46, 31.61, 19.74, 18.72, 13.37. (The presence of five sp^2 signals for the vinyl arene instead of the expected six suggests that two of the signals are isochronous.)

IR (thin film NaCl): 3425, 2958, 2870, 2836, 1608, 1511, 1466, 1297, 1250.

HRMS (ESI) *m/z* 243.137 [$(M + Na)^+$; calcd for $C_{14}H_{26}O_2$: 243.136].

Chiral HPLC analysis of the corresponding chloroacetate (**5a**) (Chiralcel OJ, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)- **5a**] = 19.8 min; t_R[(*S*)- **5a**] = 26.7 min.

$[\alpha]_D$ = –4.44 (25 ºC, 589 nm, 0.90 g/100 mL, $CHCl_3$).



(*E*)-1-(4-Chloro-phenyl)-2,4-dimethyl-pent-1-en-3-ol (**6**).

In the reductive coupling of 1-chloro-4-propynyl-benzene[3] (75 mg, 0.5 mmol, 75 μL) and isobutyraldehyde (72 mg, 1.0 mmol, 90 μL) at −25 °C, the standard procedure was used with burst addition of the aldehyde over 8 h (10 μl portions). Silica gel chromatography afforded **6** as a clear oil (83 mg, 75% yield, 83% ee, >95:5 regioselectivity). R_f = 0.45 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9, 2H); 7.21 (d, *J* = 9, 2H); 6.41 (s, 1H); 3.79 (d, *J* = 7.5, 1H); 1.89 (sept., *J* = 7, 1H); 1.84 (s, 3H); 1.03 (d, *J* = 7, 3H); 0.89 (d, *J* = 7, 3H).

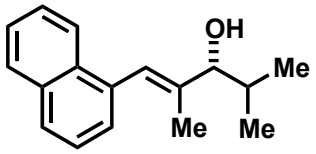
^{13}C NMR (500 MHz, $CDCl_3$) δ 140.6, 136.2, 132.3, 130.5, 128.5, 125.8, 84.1, 31.6, 19.8, 18.4, 13.6.

IR (thin film NaCl): 3406, 2960, 2871, 1491, 1467, 1366.

HRMS (EI) *m/z* 224.096 [M^+; calcd for $C_{13}H_{17}ClO$: 224.096].

Chiral HPLC analysis of the corresponding chloroacetate (**6a**) (Chiralcel OD, hexanes: 2-propanol, 99.5:0.5, 1 mL/min): t_R[(*R*)-**6a**] = 10.9 min; t_R[(*S*)-**6a**] = 14.3 min.

$[\alpha]_D$ = –13.33 (25 ºC, 589 nm, 1.05 g/100 mL, $CHCl_3$).



(*E*)-2,4-Dimethyl-1-naphthalen-1-yl-pent-1-en-3-ol (**7**).

In the reductive coupling of 1-prop-1-ynyl-napthalene[3] (166 mg, 1 mmol, 164 μL) and isobutyraldehyde (144 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded **7** as a clear oil (223 mg, 93% yield, 90% ee, >95:5 regioselectivity). R_f = 0.16 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 - 7.98 (m, 1H); (7.86 – 7.88 (m, 1H); 7.78 (d, *J* = 8, 1H); 7.45 – 7.51 (m, 3H); 7.34 (d, *J* = 7, 1H); 6.91 (s, 1H), 3.98 (d, *J* = 7, 1H); 1.98 (sept, *J* = 6.5, 1H); 1.72 (s, 3H); 1.70 (d, *J* = 3, 1H); 1.13 (d, *J* = 6.5, 3H); 1.03 (d, *J* = 6.5, 3H).

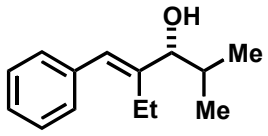
^{13}C NMR (500 MHz, $CDCl_3$) δ 141.68, 135.10, 133.74, 132.19, 128.60, 127.30, 126.85, 126.01, 125.92, 125.46, 125.18, 125.01, 83.82, 31.62, 19.94, 18.54, 13.49.

IR (thin film NaCl): 3580, 3407, 3058, 2958, 2870, 1927, 1816, 1655, 1591, 1507, 1467, 1385.

HRMS (ESI) *m/z* 263.1397 [$(M + Na)^+$; calcd for $C_{17}H_{20}O$: 263.1406].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**7**] = 9.8 min; t_R[(*S*)-**7**] = 11.1 min.

$[\alpha]_D$ = –21.67 (25 ºC, 589 nm, 0.30 g/100 mL, $CHCl_3$).



(*E*)-4-Benzylidene-2-methyl-hexan-3-ol (**8**).

In the reductive coupling of 1-phenyl-1-butyne (130 mg, 1 mmol, 142 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded **8** as a clear oil (166 mg, 81% yield, 93% ee, >95:5 regioselectivity). R_f = 0.28 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.36 (m, 5H); 6.49 (s, 1H); 3.92 (d, *J* = 6.5, 1H); 2.35 – 2.43 (m, 1H); 2.19 – 2.25 (m, 1H); 1.92 – 1.97 (m, 1H); 1.13 (t, *J* = 7.5, 3H); 1.02 (d, *J* = 6.5, 3H); 0.97 (d, *J* = 6.5, 3H).

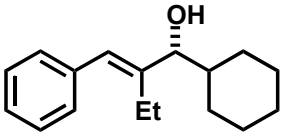
^{13}C NMR (500 MHz, $CDCl_3$) δ 146.08, 137.93, 128.83, 128.41, 126.60, 126.31, 82.05, 32.00, 21.77, 20.16, 17.80, 14.17.

IR (thin film NaCl): 3427, 3056, 3023, 2965, 2872, 1945, 1720, 1648, 1599, 1493, 1468, 1382.

HRMS (ESI) *m/z* 227.140 [$(M + Na)^+$; calcd for $C_{14}H_{20}O$: 227.141].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**8**] = 12.5 min; t_R[(*S*)-**8**] = 14.4 min.

$[\alpha]_D$ = –22.50 (25 ºC, 589 nm, 0.20 g/100 mL, $CHCl_3$).



(*E*)-2-benzylidene-1-cyclohexyl-butan-1-ol (**9**):

In the reductive coupling of 1-phenyl-1-butyne (651 mg, 5 mmol, 710 μL) and cyclohexanecarboxaldehyde (1.12 g, 10.0 mmol, 1.21 mL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded **9** as a clear oil (0.95 g, 78% yield, 89% ee, >95:5 regioselectivity). R_f = 0.24 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.36 (m, 5H); 6.45 (s, 1H); 3.93 (d, *J* = 7, 1H); 2.37 (m, 1H); 2.24 (m, 1H); 2.00 (d, *J* = 12.5, 1H); 1.55 – 1.82 (m, 6H); 1.18 – 1.29 (m, 2H); 1.13 (t, *J* = 7.5, 3H); 1.04 – 1.10 (m, 2H).

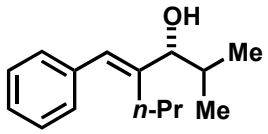
^{13}C NMR (500 MHz, $CDCl_3$) δ 145.77, 137.86, 128.83, 128.42, 128.15, 126.63, 81.71, 41.82, 30.41, 28.54, 26.71, 26.51, 26.33, 21.71, 14.26.

IR (thin film NaCl): 3407, 3055, 3023, 2927, 2851, 1599, 1493, 1448, 1308, 1261, 1173.

HRMS (ESI) *m/z* 267.173[$(M + Na)^+$; calcd for $C_{17}H_{24}O$: 267.172].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**9**] = 11.8 min; t_R[(*S*)-**9**] = 13.2 min.

$[\alpha]_D$ = –29.50 (25 ºC, 589 nm, 1.00 g/100 mL, $CHCl_3$).



(*E*)-4-Benzylidene-2-methyl-heptan-3-ol (**10**).

In the reductive coupling of 1-phenyl-1-pentyne (144 mg, 1 mmol, 159 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of the aldehyde over 8 h. Silica gel chromatography afforded **10** as a clear oil (156 mg, 72% yield, 92% ee, >95:5 regioselectivity). R_f = 0.28 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.35 (m, 2H); 7.22 – 7.27 (m, 3H), 6.50 (s, 1H), 3.90 (d, *J* = 6.5, 1H); 2.28 – 2.33 (m, 1H); 2.12 – 2.17 (m, 1H); 1.93 (sept, *J* = 7, 1H); 1.50 – 1.56 (m, 2H); 1.01 (d, *J* = 7, 3H); 0.95 (d, *J* = 7, 3H); 0.92 (t, *J* = 7, 3H).

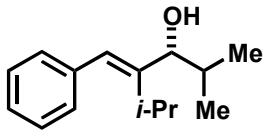
^{13}C NMR (500 MHz, $CDCl_3$) δ 144.81, 138.02, 128.83, 128.40, 128.11, 126.57, 82.14, 32.01, 31.15, 22.74, 20.16, 17.78, 14.76.

IR (thin film NaCl): 3431, 3056, 3024, 2959, 2871, 1944, 1649, 1600, 1576, 1493, 1468, 1380.

HRMS (ESI) *m/z* 241.156 [(M + Na)$^+$; calcd for $C_{15}H_{22}O$: 241.156].

Chiral GC analysis (Chiraldex B-PH, column = 125 °C, injector = 200 °C, flow (H_2) = 3 mL/min): t_R[(*R*)-**10**] = 74.7 min; t_R[(*S*)-**10**] = 72.5 min.

$[\alpha]_D$ = –26.55 (25 ºC, 589 nm, 1.13 g/100 mL, $CHCl_3$).



(*E*)-4-Benzyl-2,5-dimethyl-hexan-3-ol (**11**).

In the reductive coupling of 3-methyl-1-phenyl-but-1-yne[4] (50 mg, 0.35 mmol, 60 μL) and isobutyraldehyde (50 mg, 0.7 mmol, 70 μL) at 0 °C, the standard procedure was used with burst addition of the aldehyde over 7 h (10 μL portions). Silica gel chromatography afforded a clear oil found to be a 5:4 mixture of reductive (**11**) and alkylative[5] (**11a**) coupling products by ^{1}H NMR (47 mg, 58% combined yield, 92% ee reductive, >95:5 regioselectivity). Further purification by silica gel chromatography provided pure **11** for analysis. R_f (**11**) = 0.23 (10:1 hexanes: ethyl acetate). R_f (**11a**) = 0.28 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.36 (m, 5H); 6.62 (s, 1H); 3.89 (d, J = 6.5, 1H); 3.10 (sept, *J* = 7, 1H); 2.00 (sept, *J* = 7, 1H); 1.20 (d, *J* = 7, 3H); 1.10 (d, *J* = 6.5, 3H); 1.04 (d, *J* = 7, 3H); 0.95 (d, *J* = 7, 3H).

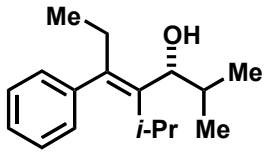
^{13}C NMR (500 MHz, $CDCl_3$) δ 150.52, 138.10, 128.96, 128.32, 126.61, 125.31, 75.67, 33.51, 28.76, 21.87, 21.66, 20.47, 18.48.

IR (thin film NaCl): 3444, 3080, 3056, 3023, 2960, 2871, 1600, 1576, 1494, 1465, 1444, 1384, 1364, 1029, 1000.

HRMS (ESI) *m/z* 241.157 [(M + Na)$^+$; calcd for $C_{15}H_{22}O$: 241.156].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**11**] = 10.7 min; t_R[(*S*)-**11**] = 9.4 min.

$[\alpha]_D$ = +45.00 (25 ºC, 589 nm, 0.03 g/100 mL, $CHCl_3$).



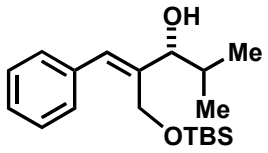
(*E*)-4-Isopropyl-2-methyl-5-phenyl-heptan-3-ol (**11a**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.34 (m, 3H); 7.08 (d, *J* = 6.5, 2H); 3.96 (d, *J* = 9, 1H); 2.75 – 2.81 (m, 1H); 2.43 – 2.50 (sept, *J* = 7, 1H); 2.25 – 2.33 (m, 1H); 2.17 – 2.22 (m, 1H); 1.15 (d, *J* = 6.5, 3H); 0.96 (d, *J* = 7, 3H); 0.93 (d, *J* = 7, 3H); 0.86 (d, *J* = 7, 3H); 0.83 (t, *J* = 7.5, 3H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 143.81, 142.10, 141.59, 128.85, 128.06, 126.28, 76.56, 33.58, 31.41, 28.49, 22.61, 22.15, 20.83, 20.73, 12.58.

IR (thin film NaCl): 3462, 3077, 3056, 3018, 2959, 2932, 2872, 1598, 1490, 1465, 1441, 1382, 1363, 1255, 1101, 1075.

HRMS (ESI) *m/z* 269.187 [$(M + Na)^+$; calcd for $C_{17}H_{26}O$: 269.188].



(*Z*)-2-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methyl-1-phenyl-pent-1-en-3-ol (**12**).

In the reductive coupling of *tert*-butyl-dimethyl-(3-phenyl-prop-2-ynyloxy)-silane (246 mg, 1 mmol, 226μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of aldehyde over 8 h. Silica gel chromatography afforded **12** as a clear oil (188 mg, 59% yield, 85% ee, >95:5 regioselectivity). R_f = 0.57 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.36 (m, 2H), 7.24 – 7.28 (m, 3H), 6.62 (s, 1H), 4.50 (d, *J* = 11.5, 1H), 4.37 (d, *J* = 11.5, 1H), 3.84 (d, *J* = 8.5, 1H), 1.98 – 2.02 (sept, *J* = 7, 1H), 1.09 (d, *J* = 7, 3H); 0.09 (m, 12H), 0.06 (d, *J* = 6, 6H).

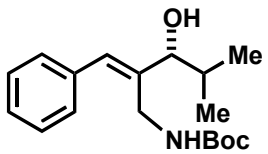
^{13}C NMR (500 MHz, $CDCl_3$) δ 140.39, 136.80, 130.44, 129.11, 128.33, 127.28, 83.96, 60.39, 32.78, 25.99, 19.99, 19.00, 18.29, -5.41.

IR (thin film NaCl): 3451, 2956, 2929, 2858, 1471, 1386, 1362, 1255.

HRMS (ESI) *m/z* 343.207 [$(M + Na)^+$; calcd for $C_{19}H_{32}O_2Si$: 343.206].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 99.5:0.5, 0.2 mL/min): t_R[(*R*)-**12**] = 53.2 min; t_R[(*S*)-**12**] = 46.9 min.

$[\alpha]_D$ = –14.81 (25 ºC, 589 nm, 1.08 g/100 mL, $CHCl_3$).



(*E*)-(1-Benzylidene-2-hydroxy-3-methyl-butyl)-carbamic acid *tert*-butyl ester (**13**).

In the reductive coupling of (3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester[6] (231 mg, 1 mmol) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL), $Ni(cod)_2$, NMDPP, and Et_3B in EtOAc were combined at room temperature and then cooled to –25 °C . The alkyne was then added as a solution in DMI (1 mL), and the aldehyde was added via syringe pump over 8 h. Silica gel chromatography afforded **13** as a white solid (183 mg, 60% yield, 96% ee, >95:5 regioselectivity). R_f = 0.17 (5:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.37 (m, 2H), 7.23 – 7.28 (m, 3H); 6.62 (s, 1H); 4.86 (bs, 1H); 4.02 (dd, *J* = 15, 7, 1H); 3.85 – 3.91 (m, 2H); 1.92 (sept, *J* = 7.5, 1H); 1.43 (s, 9H); 1.06 (d, *J* = 7, 3H); 0.91 (d, *J* = 7, 3H).

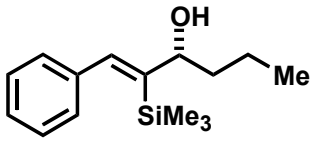
^{13}C NMR (500 MHz, $CDCl_3$) δ 156.52, 140.02, 136.79, 130.92, 128.78, 128.65, 127.39, 82.66, 79.94, 37.93, 32.47, 28.58, 20.01, 18.78.

IR (thin film NaCl): 3287, 3082, 2952, 1670, 1559, 1265, 1183.

HRMS (ESI) *m/z* 328.187 [$(M + Na)^+$; calcd for $C_{18}H_{27}NO_3$: 328.188].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**13**] = 21.7 min; t_R[(*S*)-**13**] = 27.1 min.

$[\alpha]_D$ = –2.78 (25 ºC, 589 nm, 0.90 g/100 mL, $CHCl_3$).



(Z)-1-Phenyl-2-trimethylsilanyl-hex-1-en-3-ol (**14**).

In the reductive coupling of 1-phenyl-2-(trimethylsilyl)-acetylene (87 mg, 0.5 mmol, 98 μL) and butyraldehyde (72 mg, 1.0 mmol, 90 μL) at -25 °C, the standard procedure was used with burst addition of the aldehyde over 8 h. Silica gel chromatography afforded a clear oil which was found to be a 75:25 mixture of reductive (**14**) and alkylative[5] (**14a**) allylic alcohol coupling products by ^{1}H NMR (55 mg, 43% combined yield, 92% ee reductive, >95:5 regioselectivity). Further purification by silica gel chromatography provided pure **14** for analysis. R_f (**14**) = 0.33 (10:1 hexanes: ethyl acetate). R_f (**14a**) = 0.41 (10:1 hexanes: ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H); 7.19 - 7.32 (m, 5H); 4.41 - 4.43 (m, 1H); 1.43 - 1.70 (m, 3H); 0.92 - 1.01 (m, 4H); -0.02 (s, 9H).

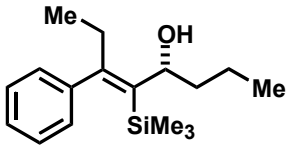
^{13}C NMR (500 MHz, $CDCl_3$) δ 147.51, 140.40, 140.25, 128.71, 127.99, 127.12, 75.78, 40.29, 19.42, 14.29, 1.05.

IR (thin film NaCl): 3364, 3057, 3024, 2958, 1593, 1491.

HRMS (ESI) *m/z* 271.149 [$(M + Na)^+$; calcd for $C_{15}H_{24}OSi$: 271.149].

Chiral HPLC analysis (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**14**] = 13.5 min; t_R[(*S*)-**14**] = 5.4 min.

$[\alpha]_D$ = +66.00 (25 ºC, 589 nm, 1.00 g/100 mL, $CHCl_3$).



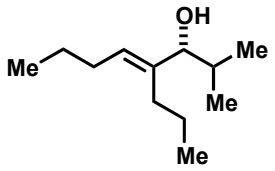
(*Z*)-6-Phenyl-5-trimethylsilanyl-octan-4-ol (**14a**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.31 (m, 3H); 7.09 (d, *J* = 6.5, 2H); 4.73 (m, 1H); 2.40 – 2.47 (m, 2H); 1.78 – 1.84 (m, 1H); 1.52 – 1.60 (m, 3H); 1.39 – 1.45 (m, 1H); 1.01 (t, *J* = 7, 3H); 0.87 (t, *J* = 6.5, 3H), –0.19 (s, 9H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 155.74, 144.84, 140.17, 129.35, 127.86, 126.97, 74.39, 39.78, 29.58, 20.16, 14.36, 12.94, 2.60.

IR (thin film NaCl): 3609, 3473, 3077, 3057m 3024, 2959, 2872, 1584, 1488, 1457, 1442, 1407, 1374, 1246, 1136. 1072, 1022.

HRMS (ESI) *m/z* 299.180 [$(M + Na)^+$; calcd for $C_{17}H_{28}OSi$: 299.180].



(*E*)-2-Methyl-4-propyl-oct-4-en-3-ol (**15**).

In the reductive coupling of 4-octyne (110 mg, 1 mmol, 146 μL) and isobutyraldehyde (114 mg, 2.0 mmol, 180 μL) at −25 °C, the standard procedure was used with syringe pump addition of aldehyde over 8 h. Silica gel chromatography afforded a clear oil which was found to be a 32:68 mixture of reductive (**15**) and alkylative[5] (**15a**) allylic alcohol coupling products by ^{1}H NMR (88 mg, 35% combined yield, 42% ee reductive). The two compounds were inseparable by silica gel chromatography. R_f = 0.38 (10:1 hexanes: ethyl acetate). Spectral data for **15** matches that previously reported.[7]

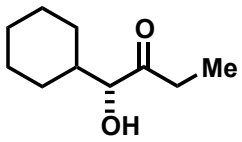
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (t, *J* = 7, 0.45H); 4.13 (d, J = 9.5, 1H); 3.65 (d, *J* = 7, 0.45H); 2.12 – 2.20 (m, 1H); 1.88 – 2.08 (m, 7.2H); 1.75 – 1.81 (m, 1H); 1.35 – 1.47 (m, 5.6H); 1.07 (d, J = 6.5, 3H); 0.90 – 0.98 (m, 10H); 0.84 (d, *J* = 7, 1.4H); 0.75 (d, 6.5, 3H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 141.36, 140.32, 134.35, 127.94, 82.96, 77.90, 34.23, 32.22, 31.81, 30.31, 30.08, 29.85, 25.02, 23.94, 23.47, 23.20, 22.18, 20.09, 20.01, 19.71, 18.28, 15.26, 14.91, 14.74, 14.47, 14.14.

HRMS (ESI) for **15a**: *m/z* 235.202[$(M + Na)^+$; calcd for $C_{14}H_{28}O$: 235.203].

Chiral GC analysis was performed on the chloroacetate derivative of **15** (**15b**): (Chiraldex B-PH column, 90 ºC for 30 min then 140 ºC for 15 min): t_R[(*R*)-**15b**] = 38.4 min; t_R[(*S*)-**15b**] = 38.9 min.

$[\alpha]_D$ = –10.00 (25 ºC, 589 nm, 0.30 g/100 mL, $CHCl_3$).



1-cyclohexyl-1-hydroxy-butan-2-one (**16**):

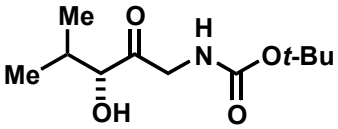
Alcohol **9** (315 mg, 1.3 mmol) was dissolved in CH_2Cl_2:MeOH (5:1, 10 mL), and the solution was cooled to –78 ºC. Ozone was bubbled through the cooled solution until a blue color was obtained (~5 min). Argon was then bubbled through for 10 min., and then methyl sulfide (6.5 mmol, 0.48 mL) was added. The reaction was allowed to warm to room temperature and stir overnight. Removal of solvent followed by column chromatography (5:1 hexanes:ethyl acetate) provided the desired α-hydroxy ketone **16** in 62% yield (138 mg, 0.81 mmol). Spectral and optical rotation data agree with those previously reported.[8]

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 1H); 3.41 (s, 1H); 2.41 – 2.57 (overlapping dq, J = 19, 7.5, 2H); 1.64 – 1.83 (m, 5H); 1.48 (dq, J = 12.5, 4, 1H); 1.17 – 1.35 (m, 5H); 1.13 (td, J = 7.5, 2, 3H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 212.99, 80.75, 41.65, 31.65, 30.30, 26.77, 26.21, 26.05, 25.32, 7.83.

Chiral GC analysis (Alltech B-PH, column = 95 °C, injector = 200 °C, flow (H_2) = 2 mL/min): t_R[(*R*)-**16**] = 32.7 min; t_R[(*S*)-**16**] = 34.2 min.

$[\alpha]_D$ = –112.5 (25 ºC, 589 nm, 1.0 g/100 mL, $CHCl_3$). Reported value: -128.03.[8a]



(3-hydroxy-4-methyl-2-oxo-pentyl)-carbamic acid *tert*-butyl ester (**17**):

Alcohol **13** (179 mg, 0.59 mmol) was dissolved in CH_2Cl_2:MeOH (5:1, 5 mL), and the solution was cooled to –78 ºC. Ozone was bubbled through the cooled solution until a blue color was obtained (~5 min). Argon was then bubbled through for 10 min., and then methyl sulfide (3.0 mmol, 0.22 mL) was added. The reaction was allowed to warm to room temperature and stir overnight. Removal of solvent followed by column chromatography (5:1 hexanes:ethyl acetate) provided the desired α-hydroxy ketone **17** in 76% yield (103 mg, 0.45 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (bs, 1H); 4.05 – 4.23 (m, 3H); 3.06 (bs, 1H); 2.14 (m, 1H); 1.46 (s, 9H); 1.12 (d, J = 7, 3H); 0.79 (d, J = 7, 3H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 208.10, 155.83, 80.36, 79.89, 47.61, 32.04, 31.80, 28.49, 22.87, 19.83, 15.18, 14.35. Spectrum showed a mixture of rotomers.

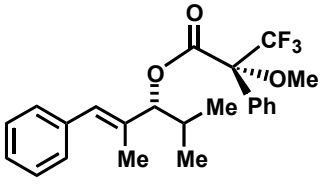
IR (thin film NaCl): 3426, 2975, 2934, 2876, 1695, 1510, 1393, 1368, 1252, 1168, 1020.

HRMS (ESI) *m/z* 254.136[$(M + Na)^+$; calcd for $C_{11}H_{24}NO_4$: 254.136].

Chiral HPLC analysis of the corresponding benzoate **17a** (Chiralcel OJ, hexanes: 2-propanol, 95:5, 0.3 mL/min): t_R[(*R*)-**17a**] = 55.3 min; t_R[(*S*)-**17a**] = 61.6 min.

$[\alpha]_D$ = –112.5 (25 ºC, 1.0 g/100 mL, $CHCl_3$).

Absolute Configuration Determination of **1** via Mosher Ester Analysis[9] (**18**).



Alcohol **1** (85 mg, 0.45 mmol, 64% ee) was dissolved in CH_2Cl_2 (10 mL). (+)-Mosher's acid (116 mg, 0.5 mmol), dicyclohexylcarbodiimide (103 mg, 0.5 mmol), and DMAP (~1 mg) were added sequentially, and the reaction was heated to reflux overnight. Once cooled completely, it was concentrated in vacuo, resuspended in hexanes:ethyl acetate (5:1), and filtered through $MgSO_4$. This filtrate was further diluted with hexanes, then washed with 1M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried and concentrated, then subjected to silica gel chromatography (50:1 hexanes: ethyl acetate) to yield **18** as a mixture of diastereomers (119 mg, 65% yield, ~85:15 diastereoselectivity). Shielding of the alkenyl group and deshielding of the

isopropyl group in the major diastereomer suggests an absolute configuration of (*R*) (see Figure 1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.54 (m, 12H); 6.61 (s, 1H); 6.53 (s, 0.17H); 5.22 (d, J = 9.5, 1H); 5.12 (d, J = 9, 0.17H); 3.60 (s, 0.59H), 3.54 (s, 3H); 2.08 (m, 1.22H); 1.85 (d, J = 1.5, 3H); 1.67 (d, J = 1.5, 0.53H); 1.03 (d, J = 7, 0.57); 0.92 (d, J = 7, 0.55); 0.91(d, J = 6.5, 3H); 0.89 (d, J = 6.5, 3H).

^{13}C NMR (500 MHz, $CDCl_3$) δ 166.31, 136.99, 134.40, 134.25, 132.79, 130.93, 130.67, 129.72, 129.67, 129.22, 129.20, 128.54, 128.49, 128.41, 128.35, 127.63 (d, *J* = 4.5), 127.49, 127.16, 127.06, 124.85, 122.56, 88.39, 88.09, 55.94, 55.59 (d, J = 4.5), 30.24, 30.04, 19.17, 19.12, 19.00, 18.78, 13.99, 13.79.

IR (thin film NaCl): 3062, 3027, 2966, 2875, 2849, 1746, 1600, 1576, 1493, 1471, 1450, 1389, 1370, 1326, 1270, 1170, 1123, 1081.

Figure 1. Determination of absolute configuration using (R)-(+)-Mosher's acid.

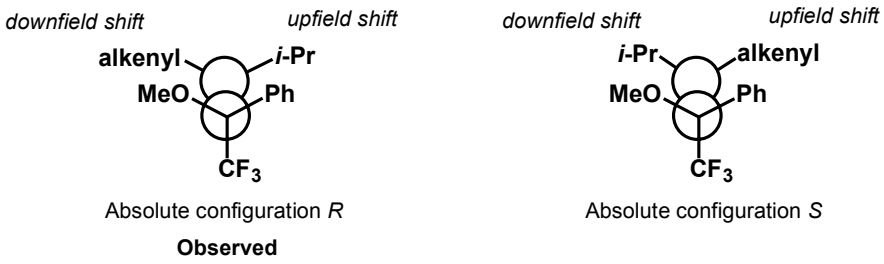


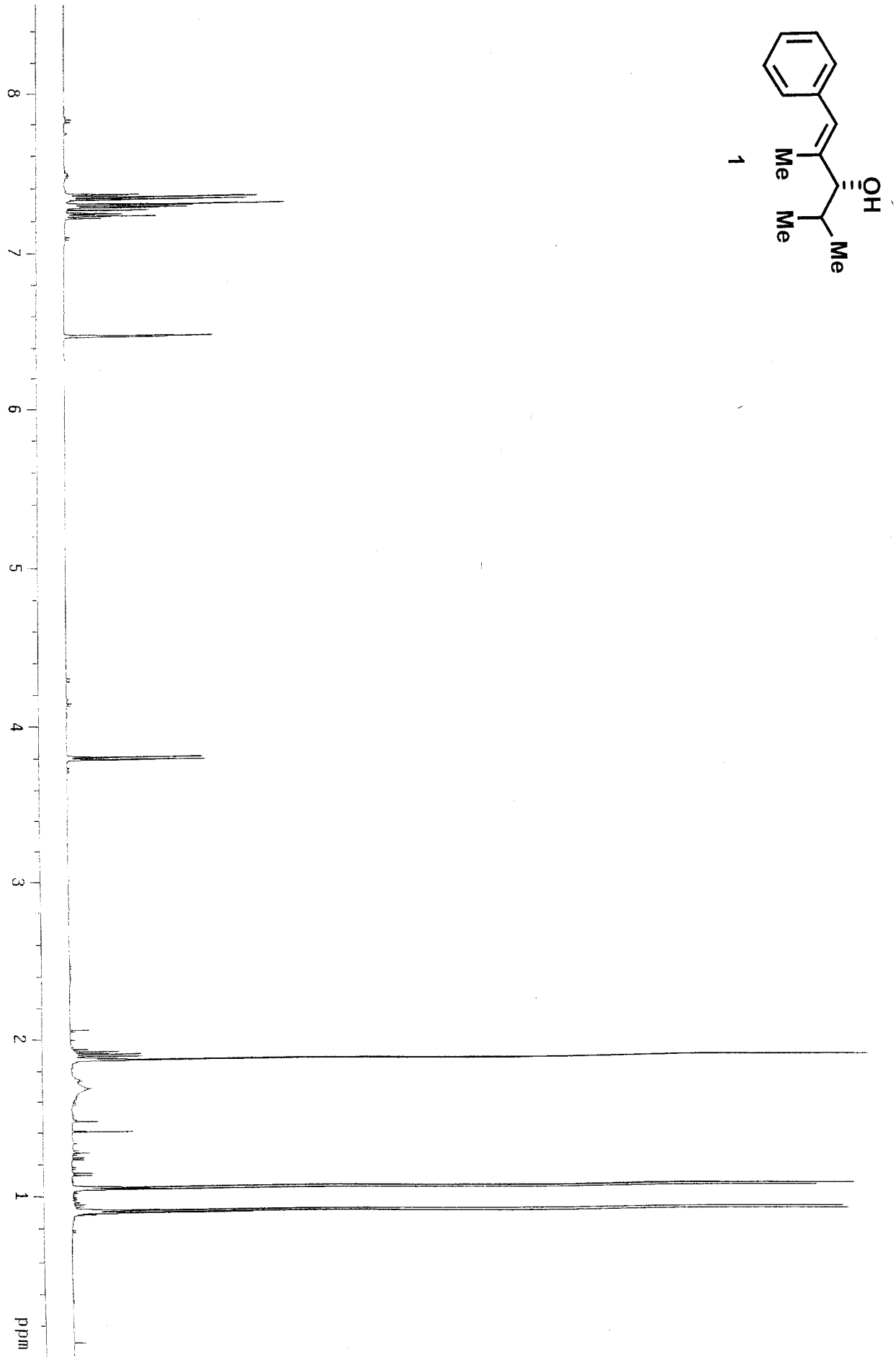
Table 1. Cooperative Effects of Solvent Composition and Mode of Aldehyde Addition On Yield and Enantioselectivity.

entry	solvent	*i*–PrCHO addition time	regioselectivity[b]	yield (%)	ee (%)[c]
1	EtOAc	<2 min	>95:5	86	82
2	EtOAc	8 h	>95:5	74	82
3[d]	EtOAc/DMI	<2 min	>95:5	94	84
4[d]	EtOAc/DMI	8 h	>95:5	95	90

[a] R^1 = Ph, R^2 = Me, R^3 = *i*–Pr. See eq. 1. Experimental procedure (see page S2 for details): A solution of $Ni(cod)_2$ (0.05 mmol), (+)–NMDPP (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc (0.5 mL) or EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to –25 °C. An alkyne (0.50 mmol) was added via syringe, and then an aldehyde (1.0 mmol) was added via syringe in the time specified. The solution was allowed to stir an additional 36 h, and silica gel chromatography afforded allylic alcohol **1**. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC or GC analysis. [d] A 1:1 ratio of EtOAc and DMI was used.

References

(1) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411.
(2) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223.
(3) Representative procedure for synthesis of alkyne coupling partners: 4-iodoanisole (5.1g, 15 mmol), palladium tetrakis(triphenylphosphine) (350 mg, 0.3 mmol), and copper iodide (29 mg, 0.15 mmol) were added to an argon-filled, 250 mL three-necked round-bottom flask. Pyrrolidine (20 mL) was added and the resulting solution cooled to -78 C. The flask was then evacuated, and 1-propyne was bubbled in slowly via syringe. After 2-3 minutes, the flask was removed from the cold bath and allowed to warm slowly to ambient temperature. Once ambient pressure had been reached, the propyne source was removed and the flask placed under an argon atmosphere. After stirring overnight, the solution was filtered through Celite and the solvent removed *in vacuo*. The residue was extracted with ether from a solution of saturated ammonium chloride, dried and condensed, and then subjected to column chromatography in 50:1 hexanes: ethyl acetate to provide 1.46g of 1-methoxy-4-propynyl-benzene as a clear liquid (75% yield).
(4) Prepared by Sonogashira cross-coupling of iodobenzene and 3-methyl-1-butyne.
(5) The result of transfer of an ethyl group (instead of H) from Et_3B.
(6) Prepared by Sonogashira cross-coupling of iodobenzene and N-*t*-butoxycarbonylprop-2-ynylamine.
(7) Colby, E. C.; Jamison, T. F. *J. Org. Chem*. **2003**, 68, 156 – 166.
(8) (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566 – 1568. (b) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308 – 5314.
(9) (a) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc*. **1973**, *95*, 512 – 519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543 – 2549.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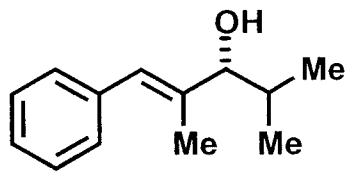

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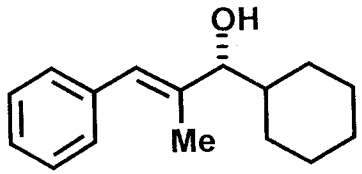

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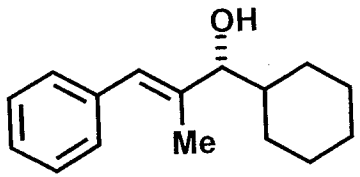

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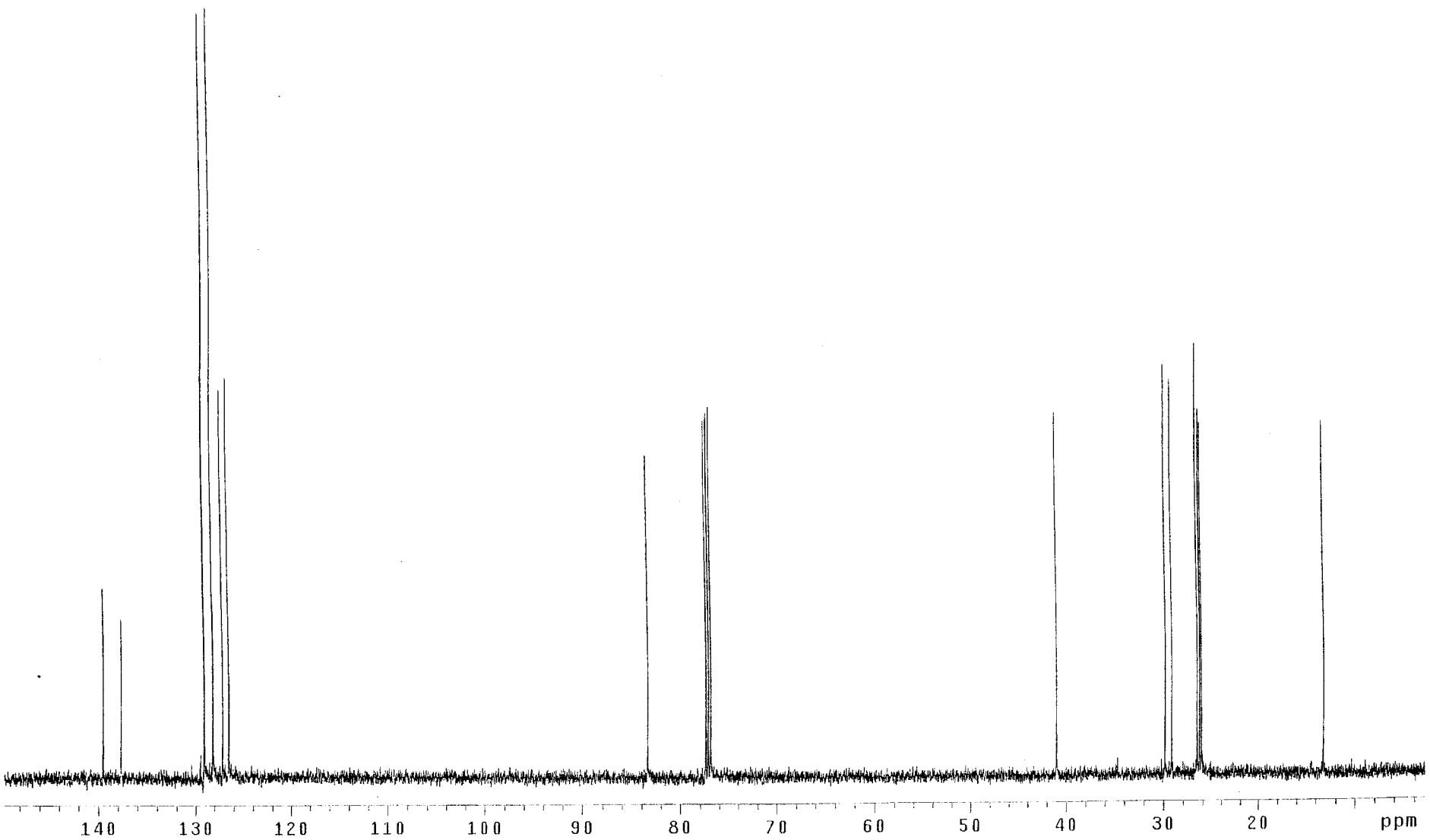
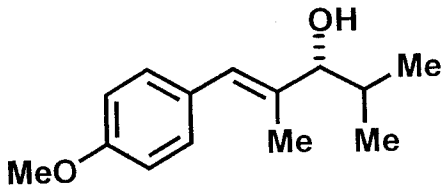
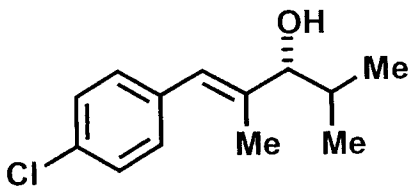




5

MeO
Me
Me
OH
Me
5
180
160
140
120
100
80
60
40
20
0
ppm



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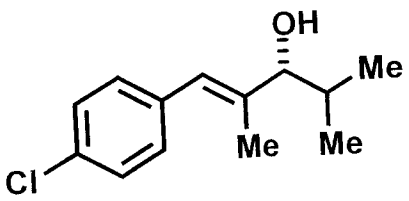

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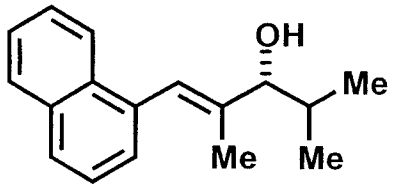

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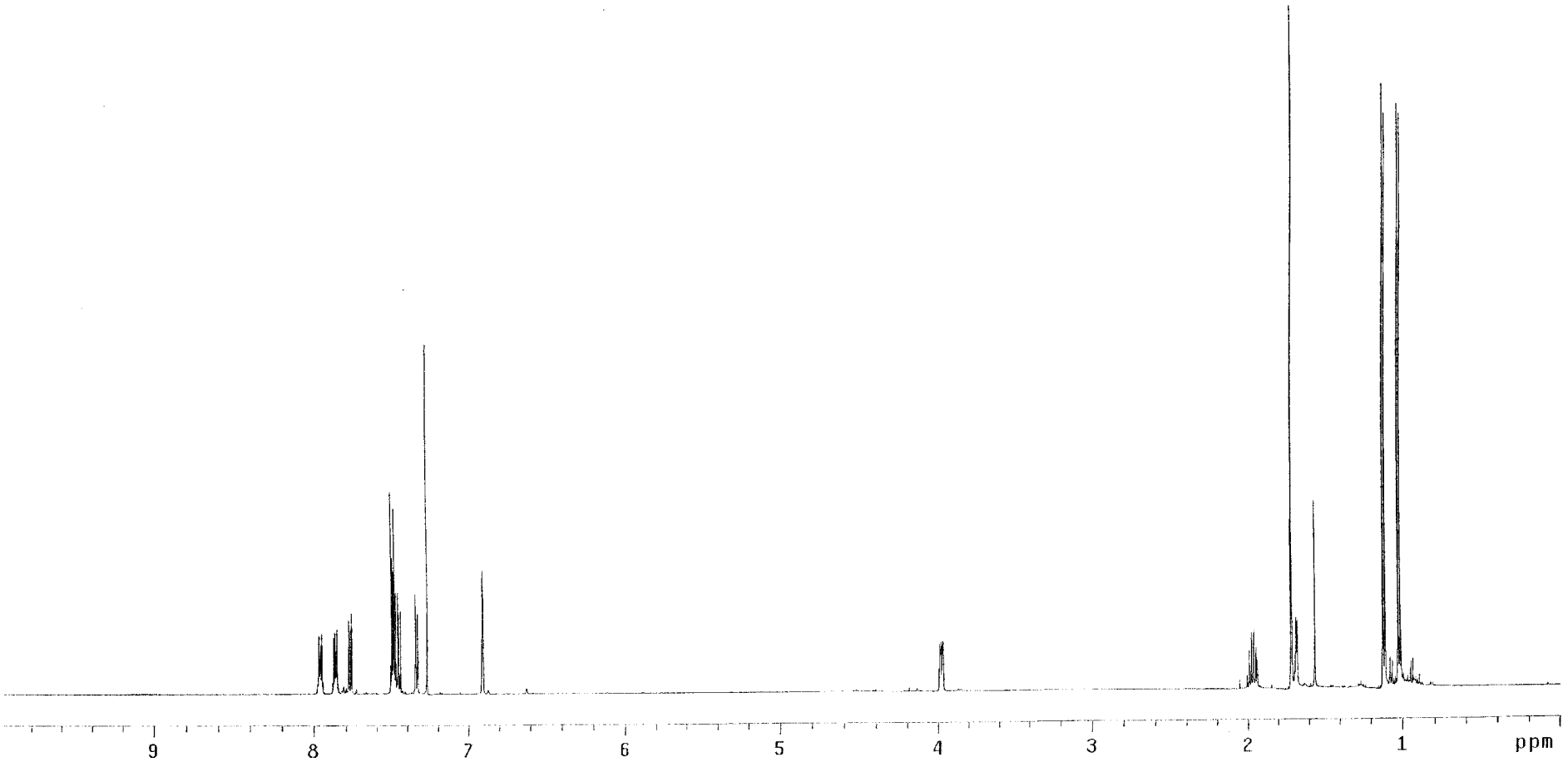

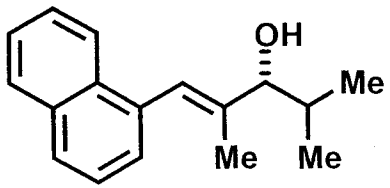

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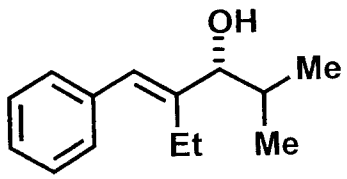

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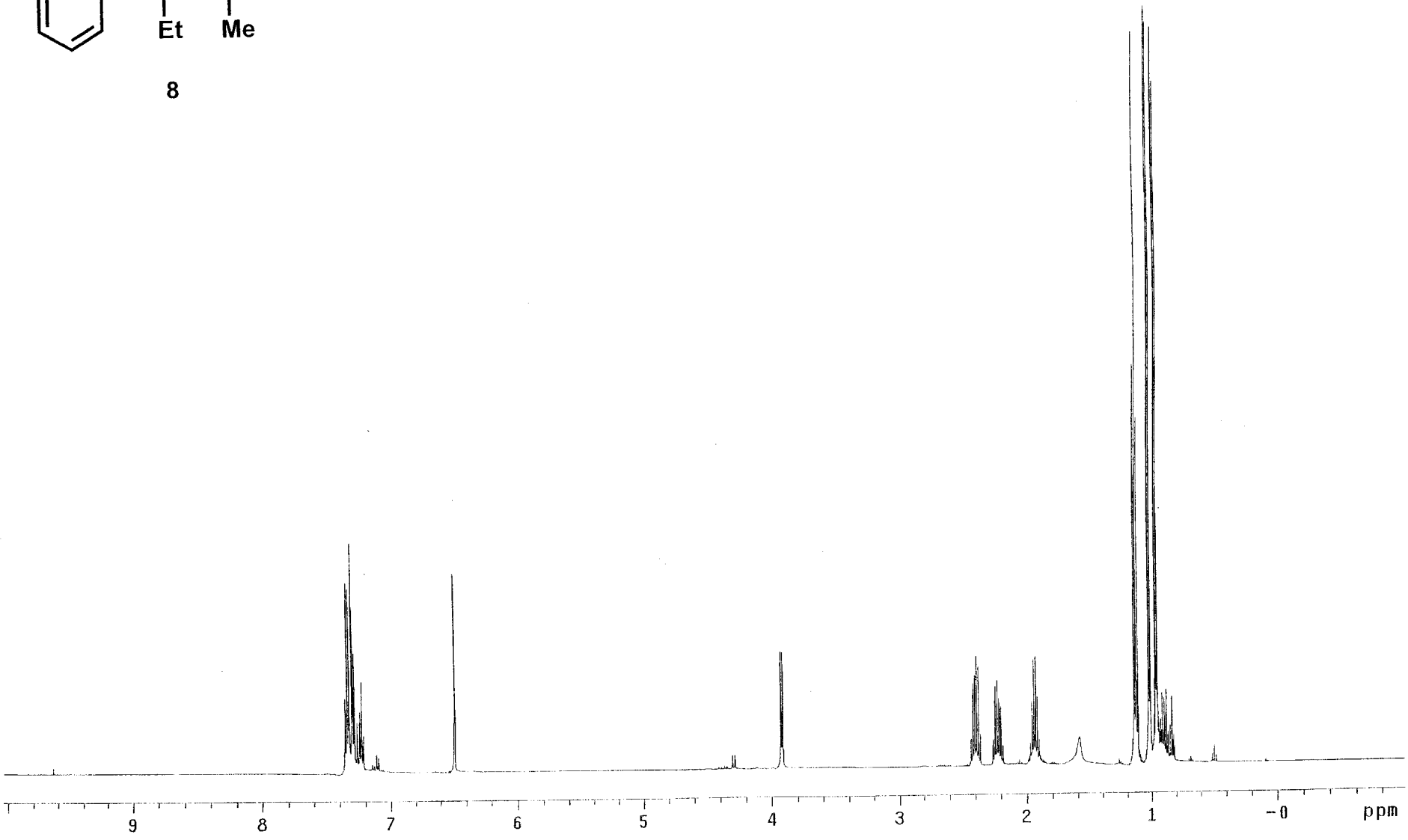

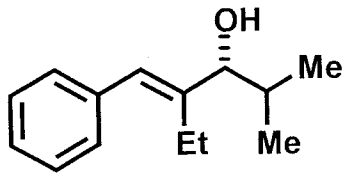

8

9
Et
OH

9
8
7
6
5
4
3
2
1
0
ppm

9
Et
OH
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120
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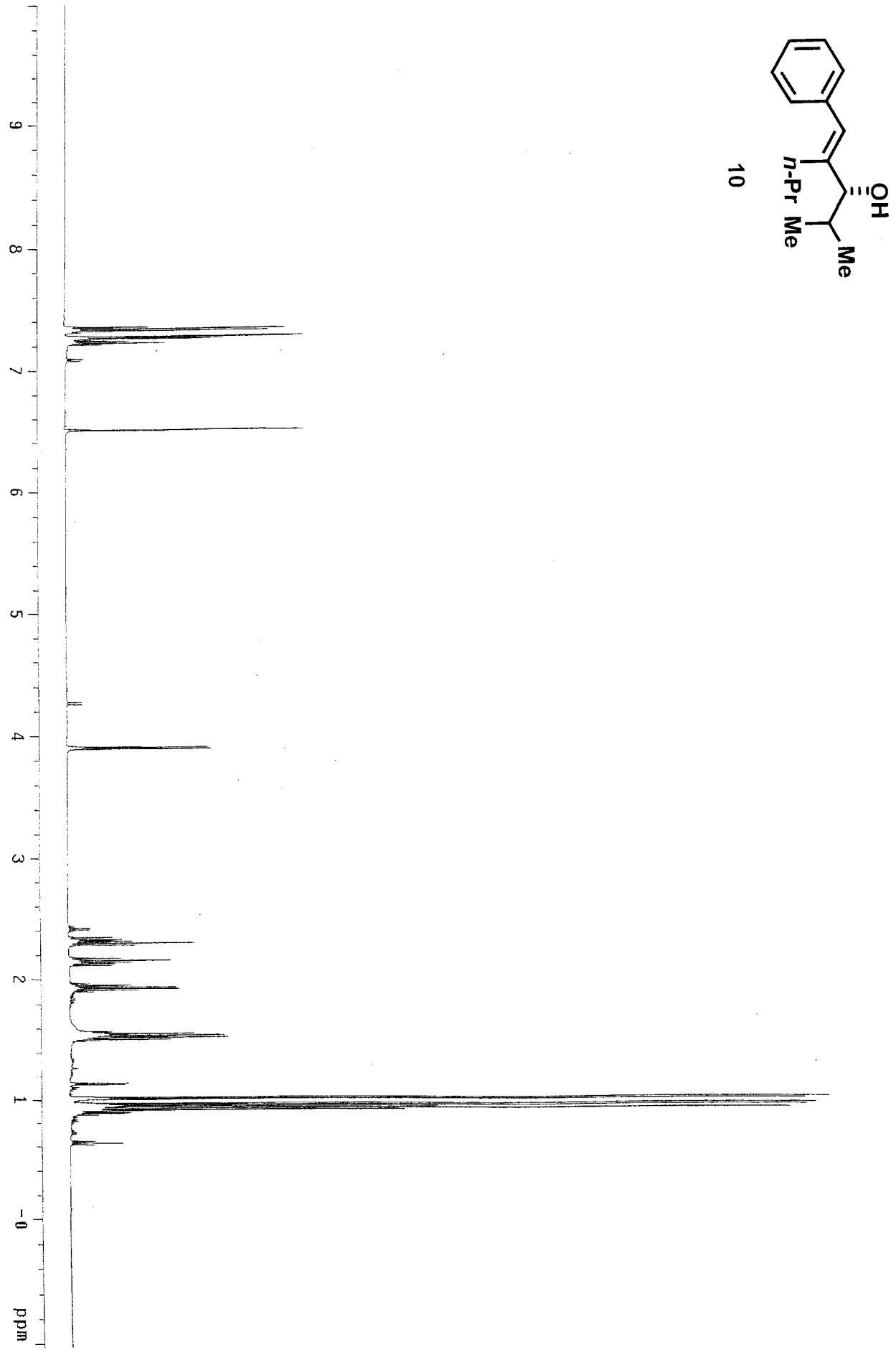
ppm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n-Pr Me
10
ppm

OH
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Me
Me
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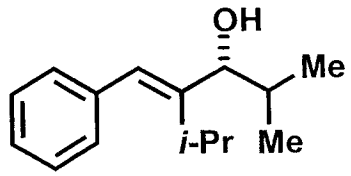
20
0
ppm

11



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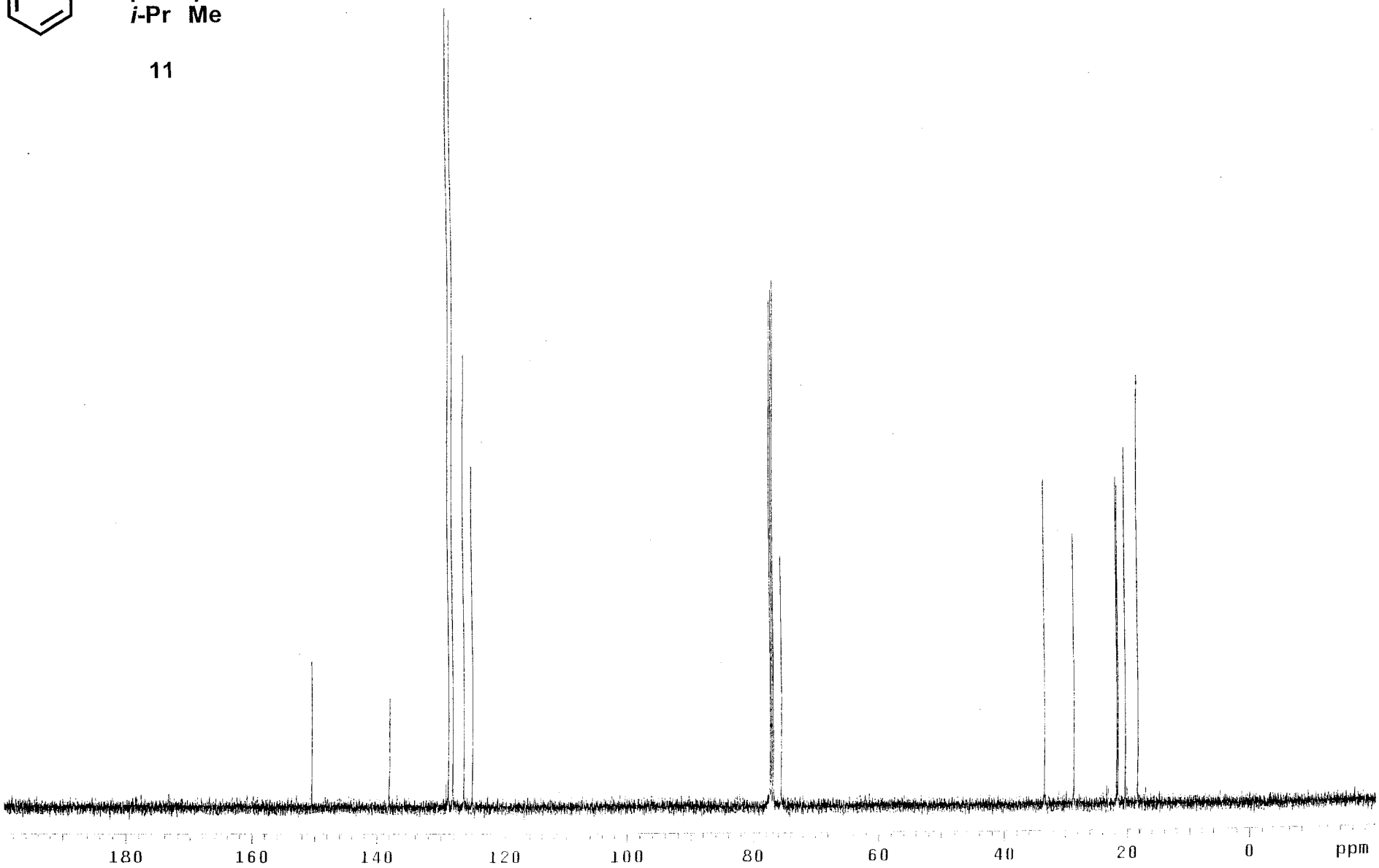

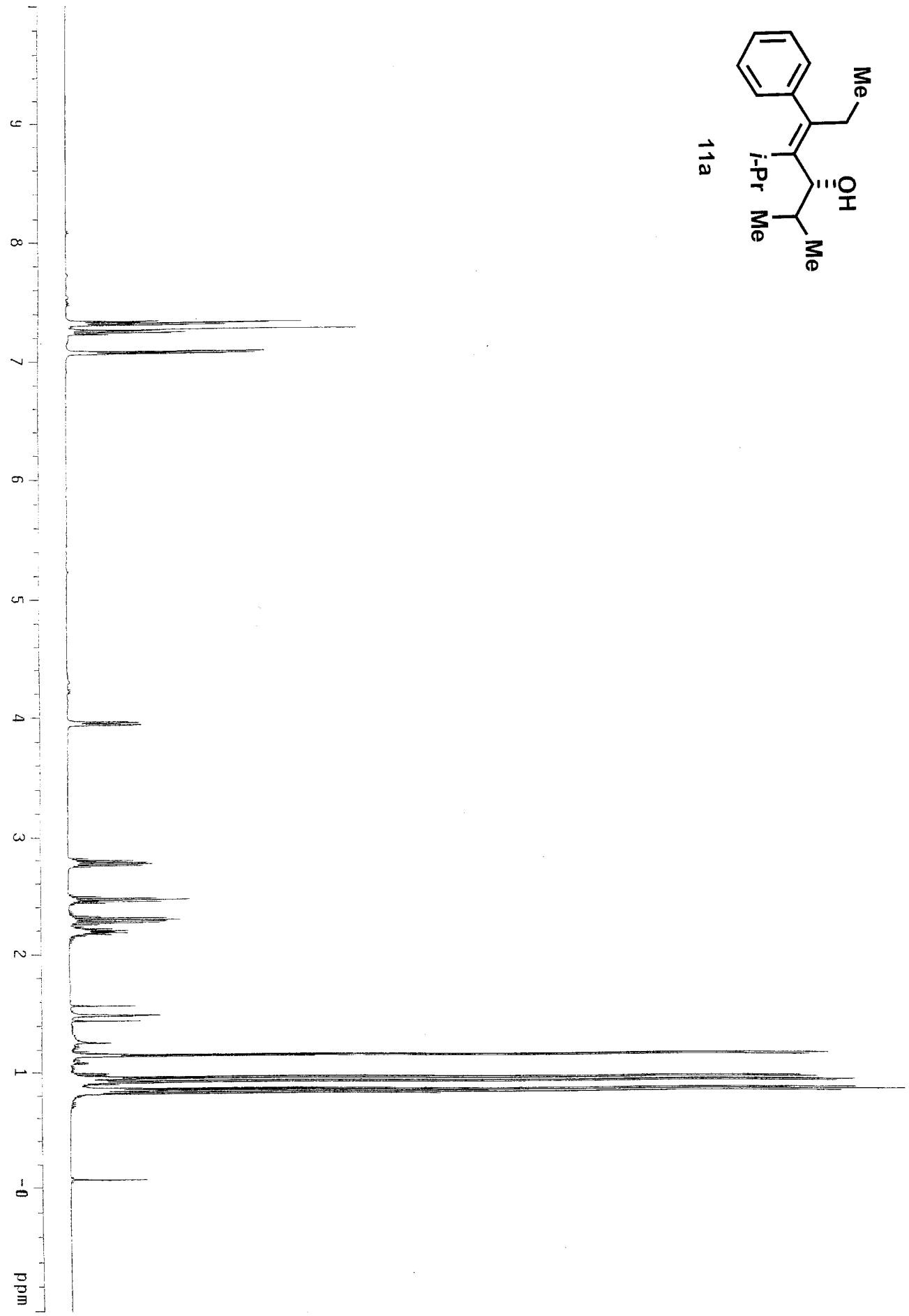
Me
OH
i-Pr Me
Me
11a
9
8
7
6
5
4
3
2
1
0
ppm

Me
OH
i-Pr
Me
Me
11a
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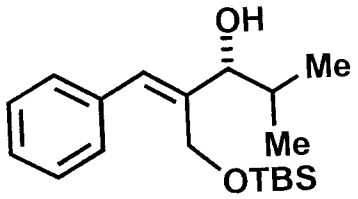

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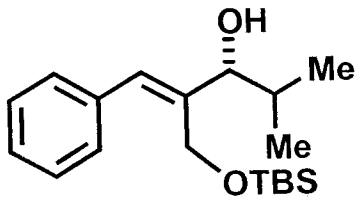

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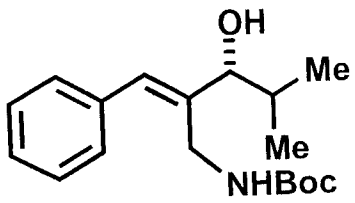

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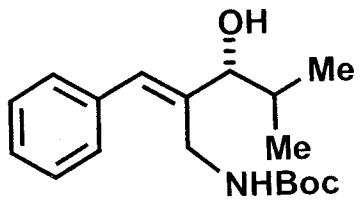

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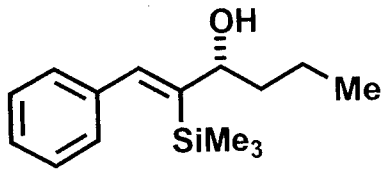

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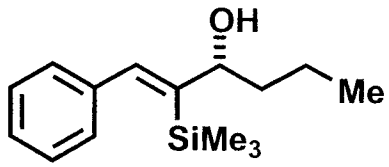

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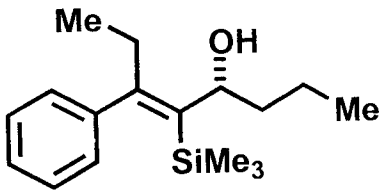

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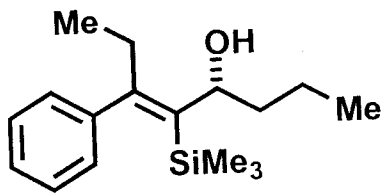

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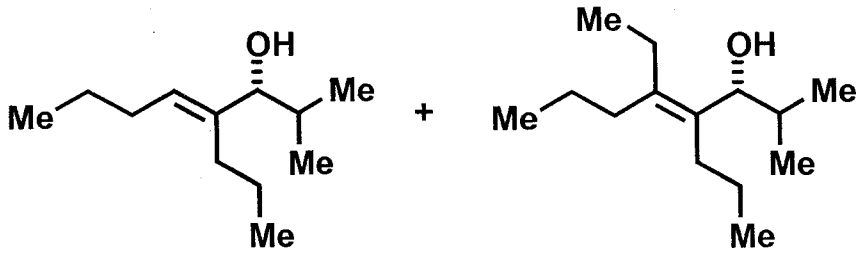

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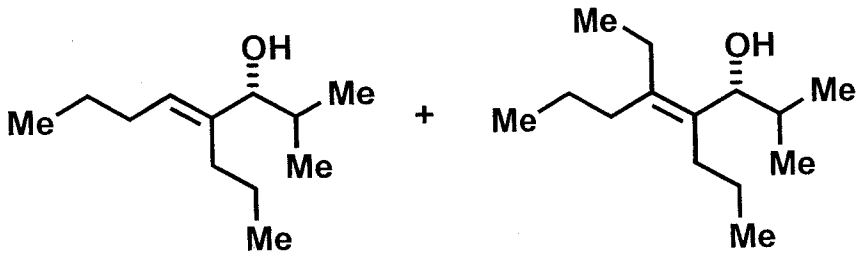
15a



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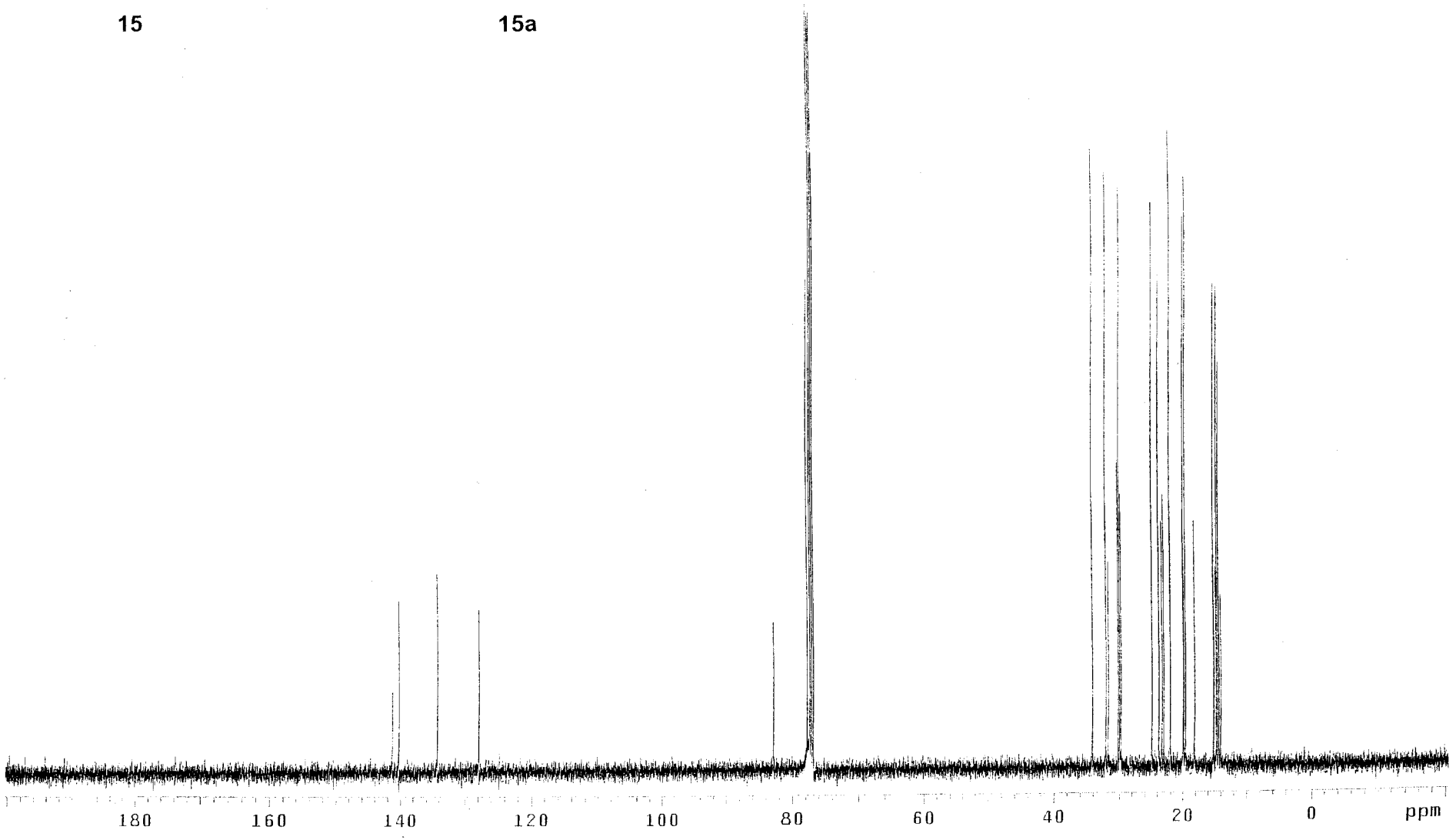

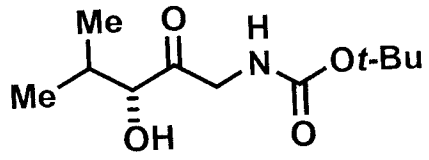

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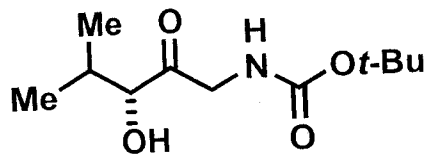

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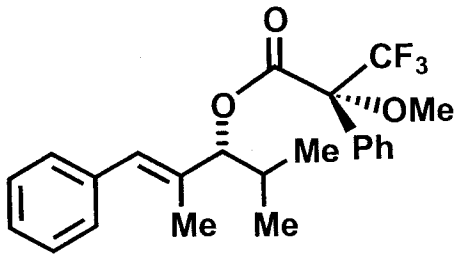

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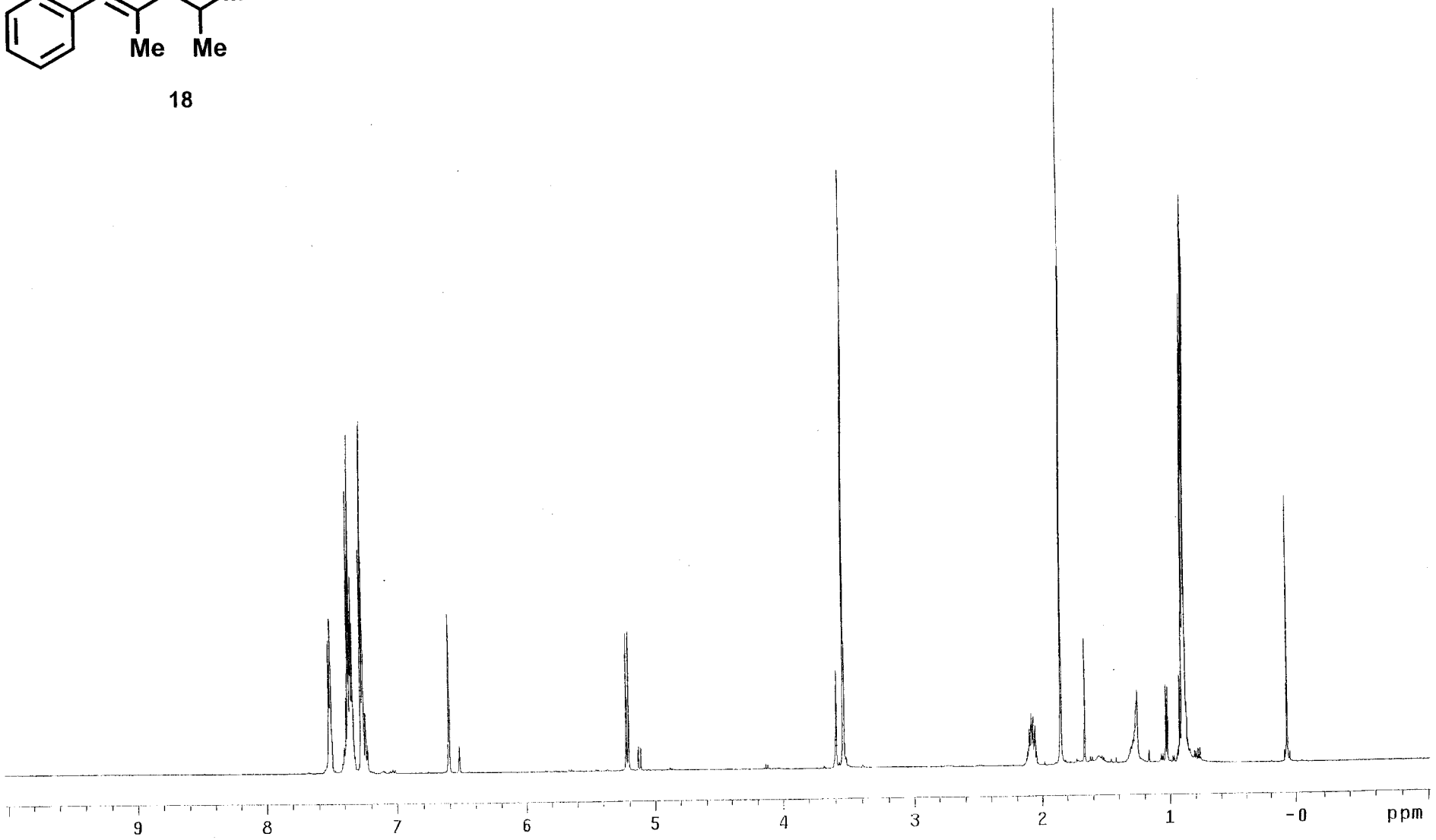

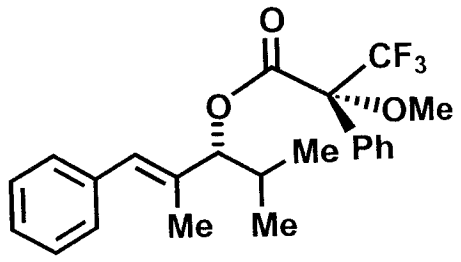

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