

Supporting Information for:

Synthesis of α,β -Unsaturated Imines *via* Ru-Catalyzed Coupling of Alcohols and Amines

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I. General Information

All glassware was either oven-dried overnight at 130 °C or flame-dried under a stream of dry nitrogen prior to use. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran and diethyl ether were freshly distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile and toluene were dried over CaH₂ and freshly distilled prior to use. All other solvents were purified in accordance with "Purification of Laboratory Chemicals".¹ Air- and moisture- sensitive reactions were performed either in a Braun LabStar glovebox under an atmosphere of nitrogen or using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing pre-coated silica gel 60 F₂₅₄ plates containing a fluorescent indicator, while preparative chromatography was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.² Unless otherwise stated, the mobile phases for column chromatography were mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient method, beginning with 100% hexanes and gradually increasing the polarity using ethyl acetate. Various stains were used to visualize reaction products, including *p*-anisaldehyde, KMnO₄, ceric ammonium nitrate and phosphomolybdic acid in ethanol stain.

¹H NMR and ¹³C NMR spectra were obtained using Bruker-300, Varian Inova-500, Varian Unity-500 or Varian Inova-600 NMR spectrometers. For ¹H NMR, chemical shifts are reported relative to residual protiated solvent peaks (δ 7.26, 2.49, 7.15 and 4.80 ppm for CDCl₃, (CD₃)₂SO, C₆D₆ and CD₃OD respectively). ¹³C NMR spectra were measured at either 125 MHz or 150 MHz on the same instruments noted above for recording ¹H NMR spectra. Chemical shifts were again reported in accordance to residual protiated solvent peaks (δ 77.0, 39.5, 128.0 and 49.0 ppm for CDCl₃, (CD₃)₂SO, C₆D₆, and CD₃OD, respectively). IR spectral data were obtained using a Bruker Vector 22 spectrometer using either a thin film or an ATR adapter. Melting points were obtained with a Mel-Temp II (Laboratory Devices, Inc.) melting point apparatus. Optical rotation measurements were performed using a Rudolph Research Autopol III Polarimeter. Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-9974839, CHE-9304546, CHE-9208463, CHE-9629688) and the University of Wisconsin, as well as the NIH (RR08389-01).

Most of the allylic alcohols were commercially available from the Aldrich Chemical Company and were used without further purification. Milstein's PNN catalyst **1d** was purchased from Strem Chemical and used without further purification. Milstein's PNP catalyst was synthesized according to literature procedure.³

II. Preparation of Allylic Alcohol Substrates

Compound 3c. NaI (4.57 g, 30.3 mmol) was suspended in 100 mL of dry THF. Triethyl phosphonoacetate (6.73 g, 30.3 mmol) was added and the resulting solution was cooled to 0 °C. An aliquot of 1,8-diazabicycloundec-7-ene (DBU, 30.3 mmol, 4.61 g) was added and the reaction was stirred for 30 min at 0 °C. The aldehyde (30.3 mmol) was added dropwise over 10 min and the reaction mixture was stirred until TLC indicated complete conversion of the starting material. The reaction was quenched with 100 mL of saturated NH₄Cl, and the aqueous mixture was extracted with 2 x 100 mL portions of EtOAc, the combined organics dried over MgSO₄ and the volatiles removed *in vacuo*. The crude product was purified using silica column chromatography (gradient 100:0 to 95:5 hexanes/EtOAc) to give the product as a clear oil (2.76 g, 59% yield, *E:Z* 4:1). The proton NMR spectrum matched that reported in the literature.⁴

A solution of ester prepared above (2.30 g, 14.8 mmol) in dry THF (55 mL) was placed in an acetonitrile/dry ice bath maintained at -42 °C. A 1.5 M solution of DIBAL-H in toluene (21.0 mL, 32.5 mmol) was added slowly added dropwise in order to maintain a constant temperature. The reaction was stirred until TLC indicated complete conversion of the starting material. The reaction mixture was quenched very carefully with a solution of saturated Rochelle's salt (55 mL) and glycerol (0.2 mL/mmol DIBAL-H). The biphasic mixture was stirred overnight and then extracted with 2 x 55 mL portions of EtOAc, dried over MgSO₄, and the volatiles removed under reduced pressure. The crude alcohol was purified by silica gel chromatography (gradient of 100:0 to 80:20 hexanes/ EtOAc) to give **3c** as a clear oil in an *E:Z* ratio of 4:1 (1.16 g, 77% yield). The proton NMR spectrum matched that reported in the literature.⁵

Compound 3e. NaI (4.57 g, 30.3 mmol) was suspended in 100 mL of dry THF. Triethyl phosphonoacetate (6.73 g, 30.3 mmol) was added and the resulting solution was cooled to 0 °C. An aliquot of 1,8-diazabicycloundec-7-ene (DBU, 30.3 mmol, 4.61 g) was added and the reaction was stirred for 30 min at 0 °C. Cyclohexanone (30.3 mmol) was added dropwise over 10 min and the reaction mixture was stirred until TLC indicated complete conversion of the starting material. The reaction was quenched with 100 mL of saturated NH₄Cl, and the aqueous mixture was extracted with 2 x 100 mL portions of EtOAc, the combined organics dried over MgSO₄ and the volatiles removed *in vacuo*. The crude product was purified using silica column

chromatography (gradient 100:0 to 95:5 hexanes/EtOAc) to give the product as a clear oil (4.72 g, 94% yield). The proton NMR spectrum matched that reported in the literature.⁶

A solution of the ester described above (4.50 g, 26.8 mmol) in dry THF (100 mL) was placed in an acetonitrile/dry ice bath. A solution of 1.5 M DIBAL-H in toluene (40.0 mL, 60.0 mmol) was added dropwise in order to maintain a constant temperature. The reaction was stirred until TLC indicated complete conversion of the starting material. The reaction mixture was quenched very carefully with a solution of saturated Rochelle's salt (55 mL) and glycerol (0.2 mL/mmol DIBAL-H). The biphasic mixture was stirred overnight and then extracted with 2 x 55 mL portions of EtOAc, dried over MgSO₄, and the volatiles removed under reduced pressure. The crude alcohol was purified by silica gel chromatography (gradient of 100:0 to 80:20 hexanes/ EtOAc) to give **3e** as a clear oil (3.19 g, 94% yield). The proton NMR spectrum matched that reported in the literature.⁷

Compound 3f. NaI (4.57 g, 30.3 mmol) was suspended in 100 mL of dry THF. Triethyl phosphonoacetate (6.73 g, 30.3 mmol) was added and the resulting solution was cooled to 0 °C. An aliquot of 1,8-diazabicycloundec-7-ene (DBU, 30.3 mmol, 4.61 g) was added and the reaction was stirred for 30 min at 0 °C. Cyclopentanone (30.3 mmol) was added dropwise over 10 min and the reaction mixture was stirred until TLC indicated complete conversion of the starting material. The reaction was quenched with 100 mL of saturated NH₄Cl, and the aqueous mixture was extracted with 2 x 100 mL portions of EtOAc, the combined organics dried over MgSO₄ and the volatiles removed *in vacuo*. The crude product was purified using silica column chromatography (gradient 100:0 to 95:5 hexanes/EtOAc) to give the product as a clear oil (3.04 g, 66% yield). The proton NMR spectrum matched that reported in the literature.⁶

A solution of ester prepared above (2.80 g, 18.1 mmol) in dry THF (60 mL) was placed in an acetonitrile/dry ice bath. A solution of 1.5 M DIBAL-H in toluene (27.0 mL, 39.8 mmol) was added dropwise in order to maintain a constant temperature. The reaction was stirred until TLC indicated complete conversion of the starting material. The reaction mixture was quenched very carefully with a solution of saturated Rochelle's salt (55 mL) and glycerol (0.2 mL/mmol DIBAL-H). The biphasic

mixture was stirred overnight and then extracted with 2 x 55 mL portions of EtOAc, dried over MgSO₄, and the volatiles removed under reduced pressure. The crude alcohol was purified by silica gel chromatography (gradient of 100:0 to 80:20 hexanes/ EtOAc) to give **3f** as a clear oil (1.93 g, 95% yield). The proton NMR spectrum matched that reported in the literature.⁸

Compound 3h. The ester was prepared in the same manner as previously described to give the product as a clear oil (4.21 g, 90% yield). The proton NMR spectrum matched that reported in the literature.⁹

A solution of the ester prepared above (4.17 g, 26.6 mmol) was placed in dry THF (100 mL) and reduced as described previously for the synthesis of **3f**. The product **3h** was obtained as a clear oil (2.56 g, 84% yield). ¹H NMR (300 MHz, CDCl₃) δ 5.65 (m, 2H), 4.09 (m, 2H), 1.63 (septet, *J* = 6.7 Hz, 1H), 1.54 (t, *J* = 5.4 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 132.3, 130.2, 64.0, 41.8, 28.4, 22.5. HRMS (ESI) *m/z* calculated for C₇H₁₄O [M – H₂O]⁺ 96.0934; found 96.0925.

Compound 2b. A solution of benzylamine (1.1 g, 10.0 mol) in 5 mL of CH₂Cl₂ was treated with dropwise addition of isovaleraldehyde (0.95 g, 11.0 mmol), whereupon the reaction mixture became cloudy. MgSO₄ (2.0 g, 16.6 mmol) was added in one portion and the solution allowed to stir for 4.5 h at rt. The reaction mixture was filtered to remove the MgSO₄ and the volatiles removed under reduced pressure to give the crude imine (1.75 g, quantitative yield) as a pale yellow oil. A pure sample was obtained *via* vacuum distillation: ¹H NMR (300 MHz, CDCl₃) δ 7.79 (t, *J* = 5.2 Hz, 1H), 7.35–7.21 (m, 5H), 4.58 (s, 2H), 2.21 (t, *J* = 5.9 Hz, 2H), 1.95 (septet, *J* = 6.8 Hz, 1H), 0.96 (d, 6H, *J* = 6.6 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 139.3, 128.4, 127.8, 126.8, 65.1, 44.7, 26.3, 22.5. HRMS (ESI) *m/z* calculated for C₁₂H₁₇N [M + H]⁺ 176.1434; found 176.1435.

Compound 2d. Sodium borohydride (0.34 g, 8.9 mmol) was added in portions over 10 min to a solution of the imine **2b** (0.98 g, 5.6 mmol) in methanol (20 mL) at rt. The reaction was stirred for 45 min at rt, quenched with 4 M NaOH solution and extracted 3x with portions of diethyl ether. The combined organics were dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (gradient, 19:1 to 1:1 hexanes/EtOAc) to afford **2d** (0.14 g, 15% as a pale yellow oil). ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.19 (m, 5H), 3.79 (s, 2H), 2.64 (t, 2H, *J* = 7.5 Hz), 1.63 (septet, *J* = 6.8 Hz, 1H), 1.40 (dd, *J* = 7.7 Hz, overlapping with N-H, 3 H total), 0.88 (d, 6H, *J* = 6.6 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 140.9, 128.6, 128.3, 127.1, 54.5, 47.9, 39.5, 26.4, 23.0 HRMS (ESI) *m/z* calculated for C₁₂H₁₉N [M + H]⁺ 178.1591; found 178.1590.

III. General Procedure for Imine Preparation

The alcohol substrate (**3a-f**, 1 mmol) and the amine (**4a-e**, 1 mmol) were dissolved in deoxygenated toluene-d₈ (0.350 mL) under a nitrogen atmosphere. Milstein's PNN catalyst **1d** (0.01 mmol) was added to the reaction, followed by mesitylene (0.028 mL, 0.2 mmol) as an internal standard. The reaction mixture was refluxed under a flow of nitrogen for 24 hours. The yields were determined and calculated by using the ratio of the integrated vinyl proton(s) from the start of the reaction to the end of the reaction relative to the internal standard using ¹H-NMR with a relaxation delay of 10 seconds.

Compound 5. There was 100% conversion of the alcohol to 78% of the desired **5**. The NMR data matched that of the reported ¹H NMR spectrum of **5**.¹⁰

Compound 6. There was 100% conversion of the alcohol to 63% of the desired **6**. A pure sample for characterization was isolated by micro vacuum distillation using a Hickman head apparatus. ¹H NMR (300 MHz, CDCl₃) δ 8.27 (dt, *J* = 1.3, 9.4 Hz, 1H), 7.20 (m, 2H), 6.86 (m, 2H), 6.05 (m, 1H), 4.58 (s, 2H), 3.78 (s, 3H), 1.94 (s, 3H), 1.87 (s, 3H). ¹³C (75 MHz, CDCl₃) δ 160.1, 158.7, 147.2, 132.0, 129.3, 125.6, 114.1, 65.0, 55.5, 26.8, 18.9. HRMS (ESI) *m/z* calculated for C₁₃H₁₇ON [M + H]⁺ 204.1383; found 204.1382.

Compound 7. There was 100% conversion of the alcohol to 77% of the desired **7**. A pure sample for characterization was isolated by micro vacuum distillation using a Hickman head apparatus. ^1H NMR (500 MHz, CDCl_3) δ 8.20 (d, $J = 9.4$ Hz, 1H), 5.99 (d of septets, $J = 9.4, 1.0$ Hz, 1H), 2.97 (m, 1H), 1.91 (s, 3H), 1.79 (m, 2H), 1.66 (m, 3H), 1.49 (m, 2H), 1.31 (m, 3H). ^{13}C (125 MHz, CDCl_3) δ 157.3, 146.2, 125.9, 70.1, 34.8, 26.7, 25.8, 25.1, 18.8. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{19}\text{N}$ $[\text{M} + \text{H}]^+$ 166.1591; found 166.1588.

Compound 8. There was 95% conversion of the alcohol to 74% of the desired **8**. A pure sample for characterization was isolated by micro vacuum distillation using a Hickman head apparatus. ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, $J = 9.7$ Hz, 1H) 7.33 (m, 4H), 7.22 (tt, $J = 1.5, 6.6$ Hz, 1H), 6.06 (m, 1H), 4.33 (q, $J = 6.7$ Hz, 1H), 1.91 (d, $J = 1.0$ Hz, 3H) 1.87 (d, $J = 1.0$ Hz, 3H), 1.53 (d, $J = 6.7$ Hz, 3H). ^{13}C (125 MHz, CDCl_3) δ 158.3, 147.1, 145.5, 128.6, 127.0, 126.8, 125.7, 70.17, 26.8, 24.9, 18.9. HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{17}\text{N}$ $[\text{M} + \text{H}]^+$ 188.1434; found 188.1433.

Compound 9. There was 57% conversion of the alcohol to 22% of the desired **9**. The NMR data matched that of the reported ^1H NMR spectrum of **9**.¹¹

Compound 10. There was 100% conversion of the alcohol to 72% of the desired **10** as a 1.8:1 mixture of *E:Z* isomers. The NMR data matched that of the reported ^1H NMR spectrum of **10**.¹²

Compound 11. There was 100% conversion of the alcohol to 83% of the desired **11** as a 2:1 mixture of *E:Z* isomers. The NMR data matched that of the reported ^1H NMR spectrum of **11**.¹²

Compound 12. There was 100% conversion of the alcohol to 61% of the desired **12** as a 6:1 mixture of *E:Z* isomers. A pure sample for characterization was isolated by micro vacuum distillation using a Hickman head apparatus. *E* isomer: ^1H NMR (300 MHz, CDCl_3) δ 8.35 (dt, $J = 1.3, 9.3$ Hz, 1H), 7.28 (m, 5H), 6.09 (dt, $J = 1.1, 9.3$ Hz, 1H), 4.65 (s, 2H), 2.35 (septet, $J = 6.9$ Hz, 1H), 1.92 (d, $J = 1.3$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 6H). *E* isomer: ^{13}C (75 MHz, CDCl_3) δ 163.4, 159.0, 142.3, 131.1, 130.7, 129.5, 125.4, 68.2, 40.0, 23.6, 17.7. *Z* isomer: ^1H NMR (300 MHz, CDCl_3) δ 8.39 (m, 1H), 7.28 (m, 5H), 5.99 (m, 1H), 4.67 (s, 2H), 3.25 (septet, $J = 7.0$ Hz, 1H), 1.80 (d, $J = 1.2$ Hz, 3H), 1.07 (d, $J = 7.0$ Hz, 6H). HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{19}\text{N}$ $[\text{M} + \text{H}]^+$ 202.1591; found 202.1592.

Compound 13. There was 100% conversion of the alcohol to 70% of the desired **13**. A pure sample for characterization was isolated by micro vacuum distillation using a Hickman head apparatus. To verify the optical purity, the crude imine **13** was dissolved in CH_2Cl_2 (5 mL) and 1 M HCl (5 mL) was added. The reaction mixture was stirred for 1 h at rt. The CH_2Cl_2 layer was removed, dried over Na_2SO_4 and the organics removed under reduced pressure. The crude aldehyde was purified by silica gel chromatography (100:0 to 90:10 hexanes/EtOAc), then added to a suspension of lithium aluminum hydride (1 mmol) in dry THF (4 mL) at 0 °C. The mixture was stirred until TLC indicated complete consumption of the starting material. The reaction was quenched with 15% NaOH (1 mL), extracted with 2 x 3 mL portions of EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure to give the alcohol. The optical rotation of both the commercial (*S*)-perillyl alcohol ($[\alpha]^D = -87.2$ ($c = 0.057$ g/mL)) and the synthesized material ($[\alpha]^D = -75.6$ ($c = 0.057$ g/mL)) was measured. Boiling point: 200 °C at 0.1 mm Hg. ^1H NMR for **13** (300 MHz, CDCl_3) δ 7.92 (s, 1H), 7.28 (m, 5H), 6.21 (m, 1H), 4.74 (m, 2H), 4.67 (m, 2H), 2.61 (m, 1H), 2.24 (m, 3H), 1.90 (m, 1H), 1.75 (s, 3H), 1.47 (m, 1H), 1.29 (m, 1H). ^{13}C (75 MHz, CDCl_3) δ 165.1, 149.4, 139.9, 138.6, 138.0, 128.6, 128.0, 127.0, 109.2, 64.9, 41.3, 31.6, 27.2, 24.3, 21.0. HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{21}\text{N}$ $[\text{M} + \text{H}]^+$ 240.1747; found 240.1748.

Compound 16. There was 85% conversion of the alcohol to 46% of the desired **16**. The NMR data matched that of the reported ^1H NMR spectrum of **16**.¹³

Compound 17. There was an 86% conversion of the alcohol to 26% of the desired **17**. The NMR data match that of the reported ^1H NMR spectrum of **17**.

and

Compound 18. There was 95% conversion of the alcohol to 49% of the desired **18**. The NMR data matched that of the reported ^1H NMR spectrum of **18** and the associated amide.¹⁴

General procedure for the redox isomerization of secondary allylic alcohols to ketones. The allylic alcohol substrate (1 mmol) was added to deoxygenated toluene- d_8 (0.3 mL) under a nitrogen atmosphere. Milstein's PNN catalyst **1d** (0.01 mmol) was added to the reaction. The reaction mixture was refluxed under a flow of nitrogen for 24 hours. Desired product was purified by distillation (**19a**) or column chromatography (**20a-25a**).

Compound 19a. The NMR data matched that of the reported ^1H NMR spectrum of **19a**.¹⁵

Compound 20a. The NMR data matched that of the reported ^1H NMR spectrum of **20a**.¹⁶

Compound 21a. The NMR data matched that of the reported ^1H NMR spectrum of **21a**.¹⁷

Compound 23a. The NMR data matched that of the reported ^1H NMR spectrum of **23a**.¹⁸

Compound 24a. The NMR data matched that of the reported ^1H NMR spectrum of **24a**.¹⁹

Compound 25a. The NMR data matched that of the reported ^1H NMR spectrum of **25a**.²⁰

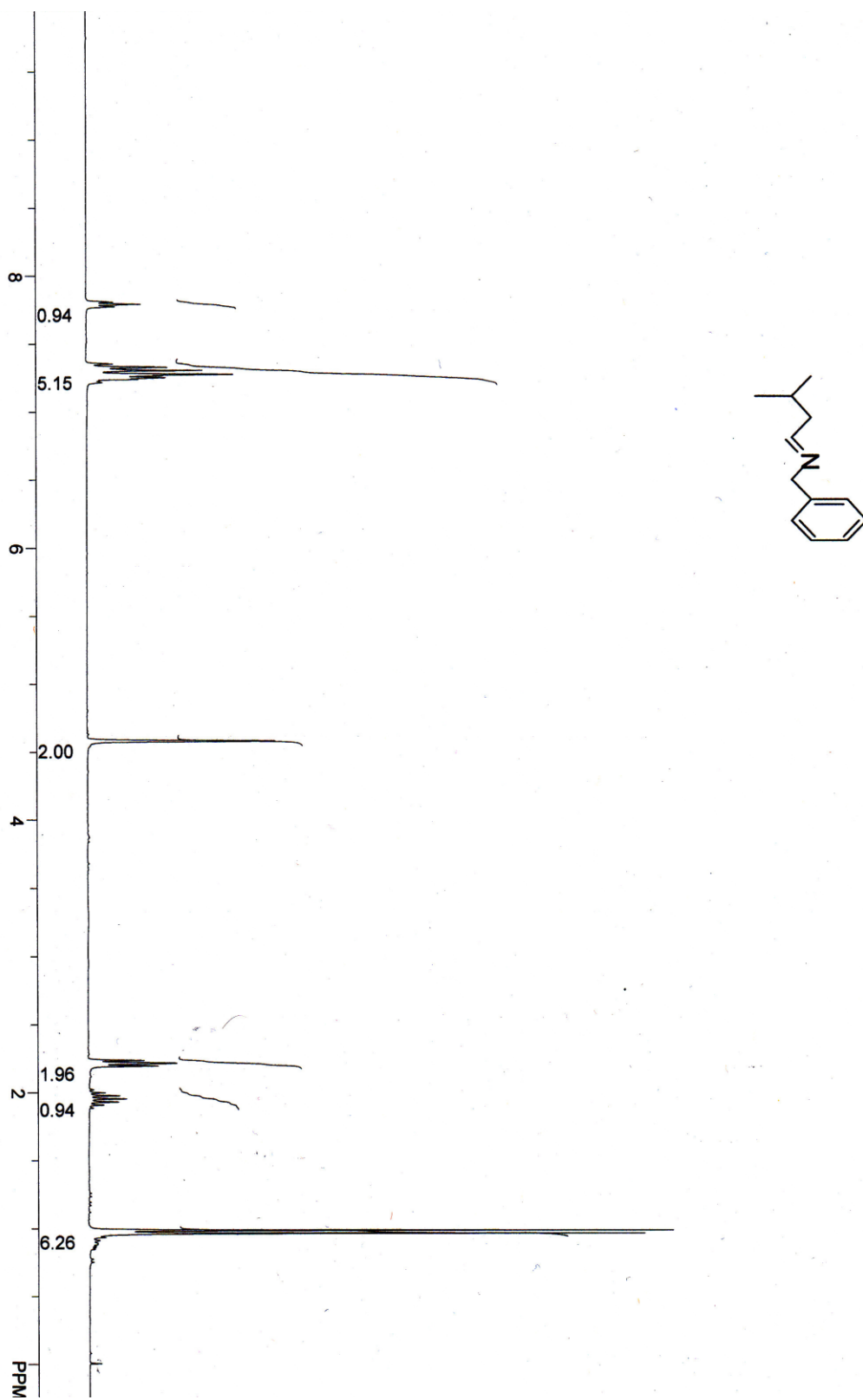
IV. References

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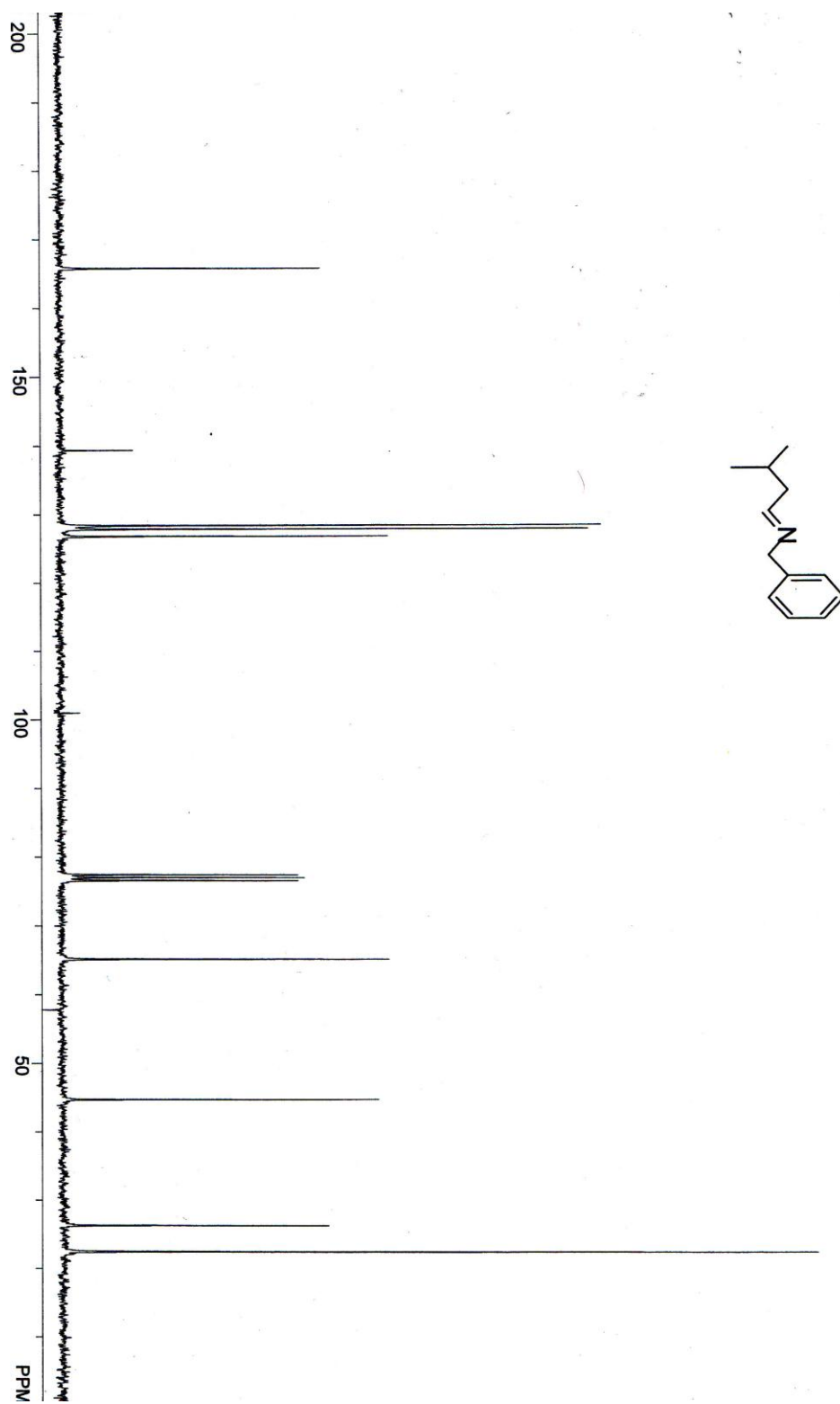
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V. NMR spectra

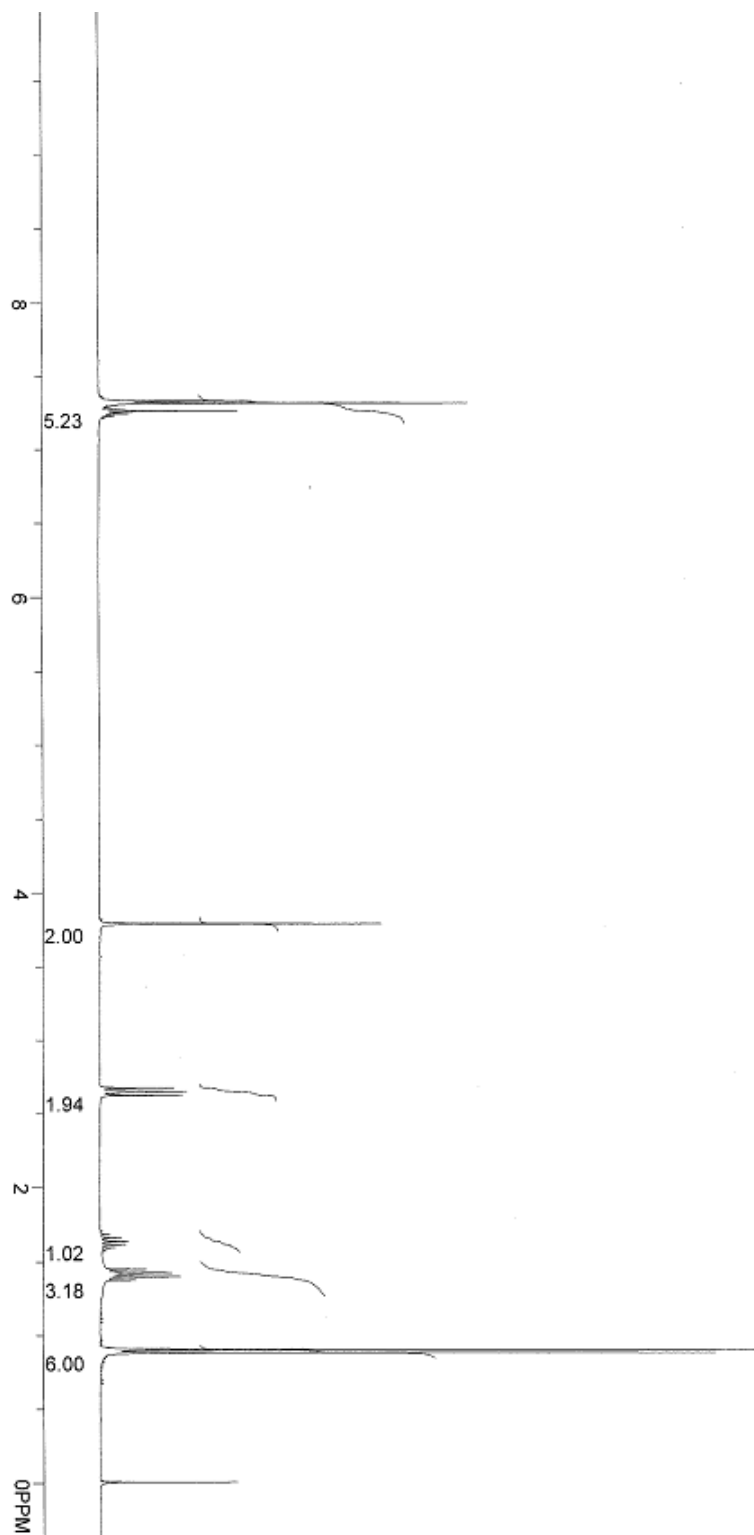
Compound 2b.



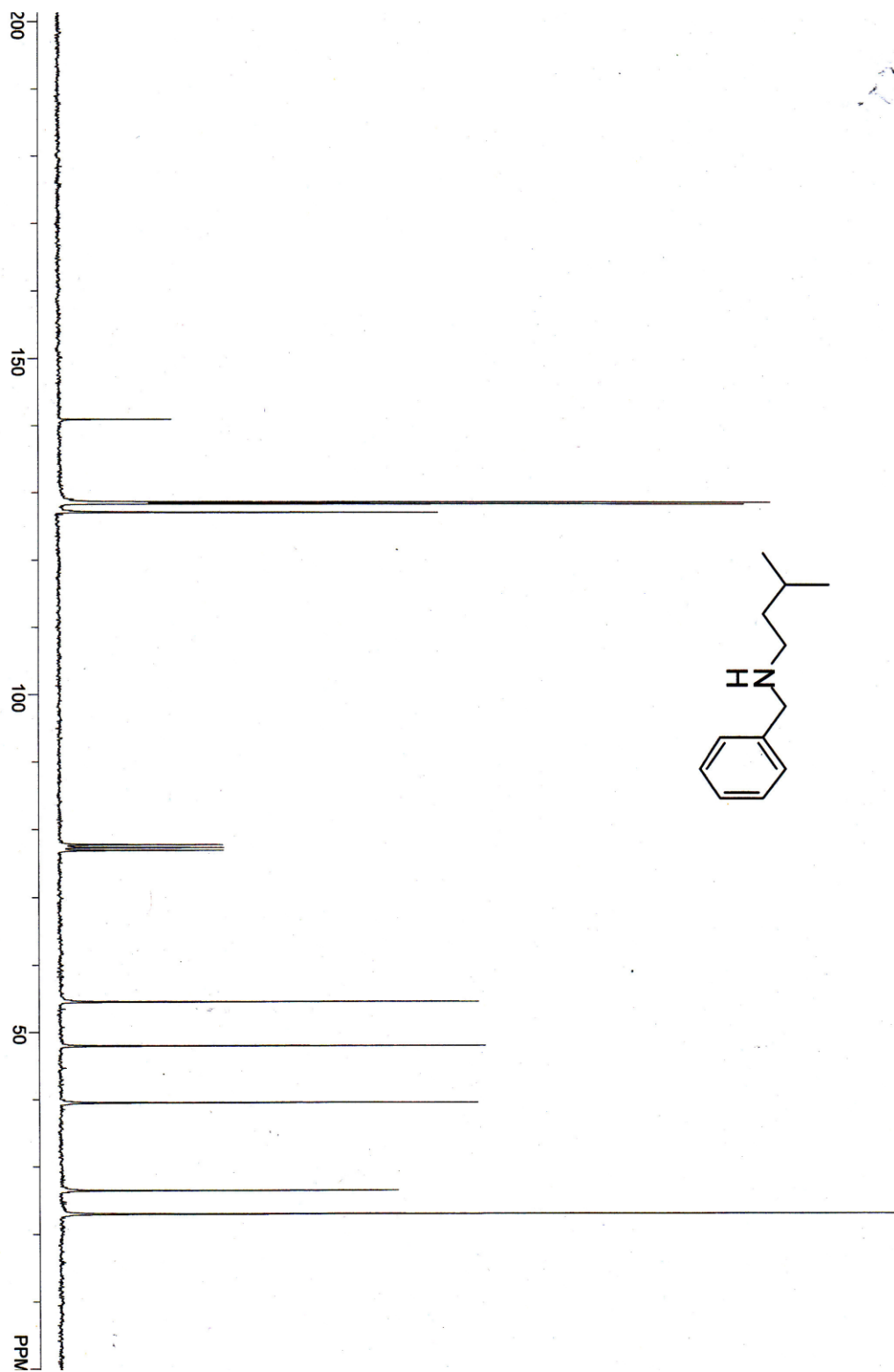
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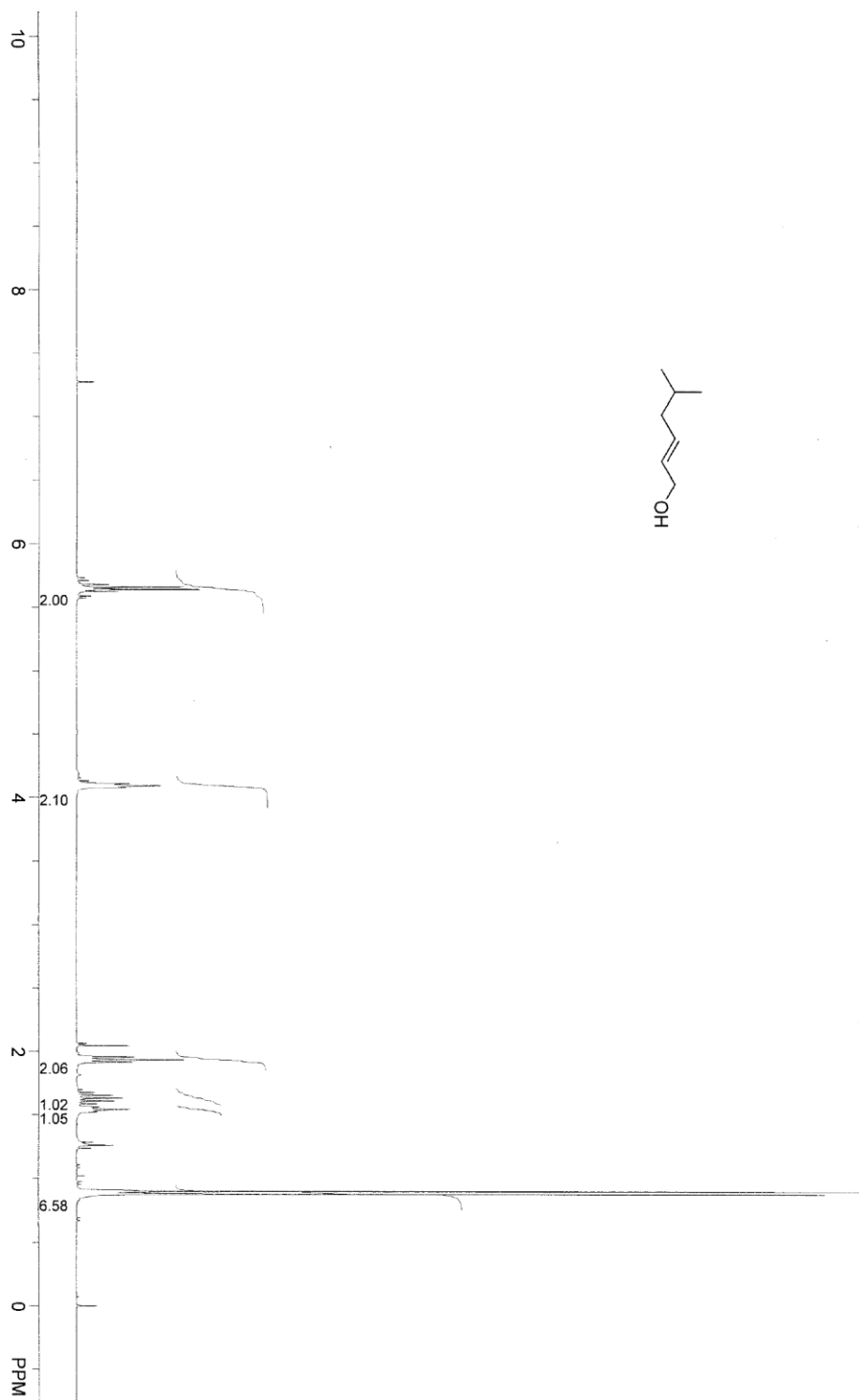
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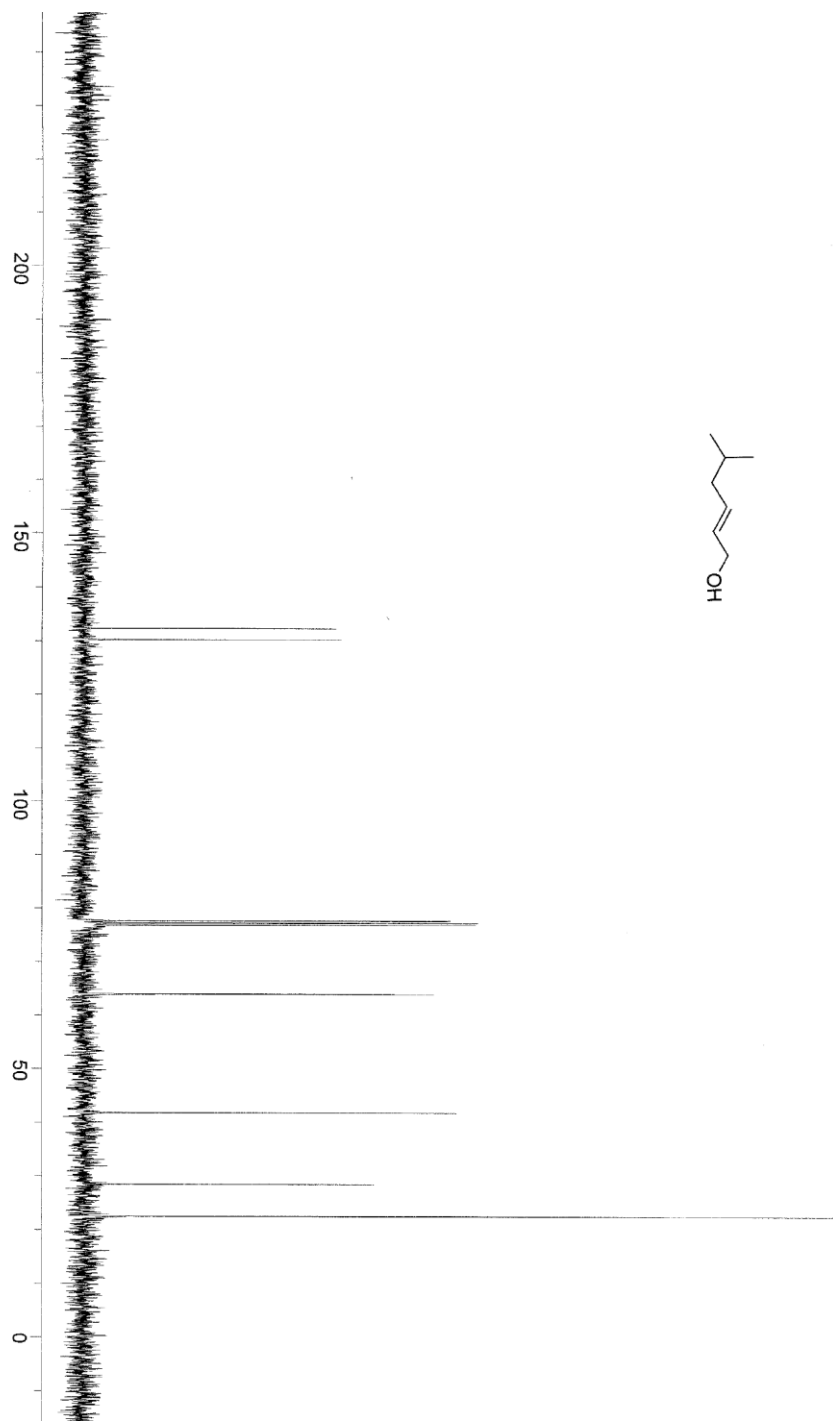
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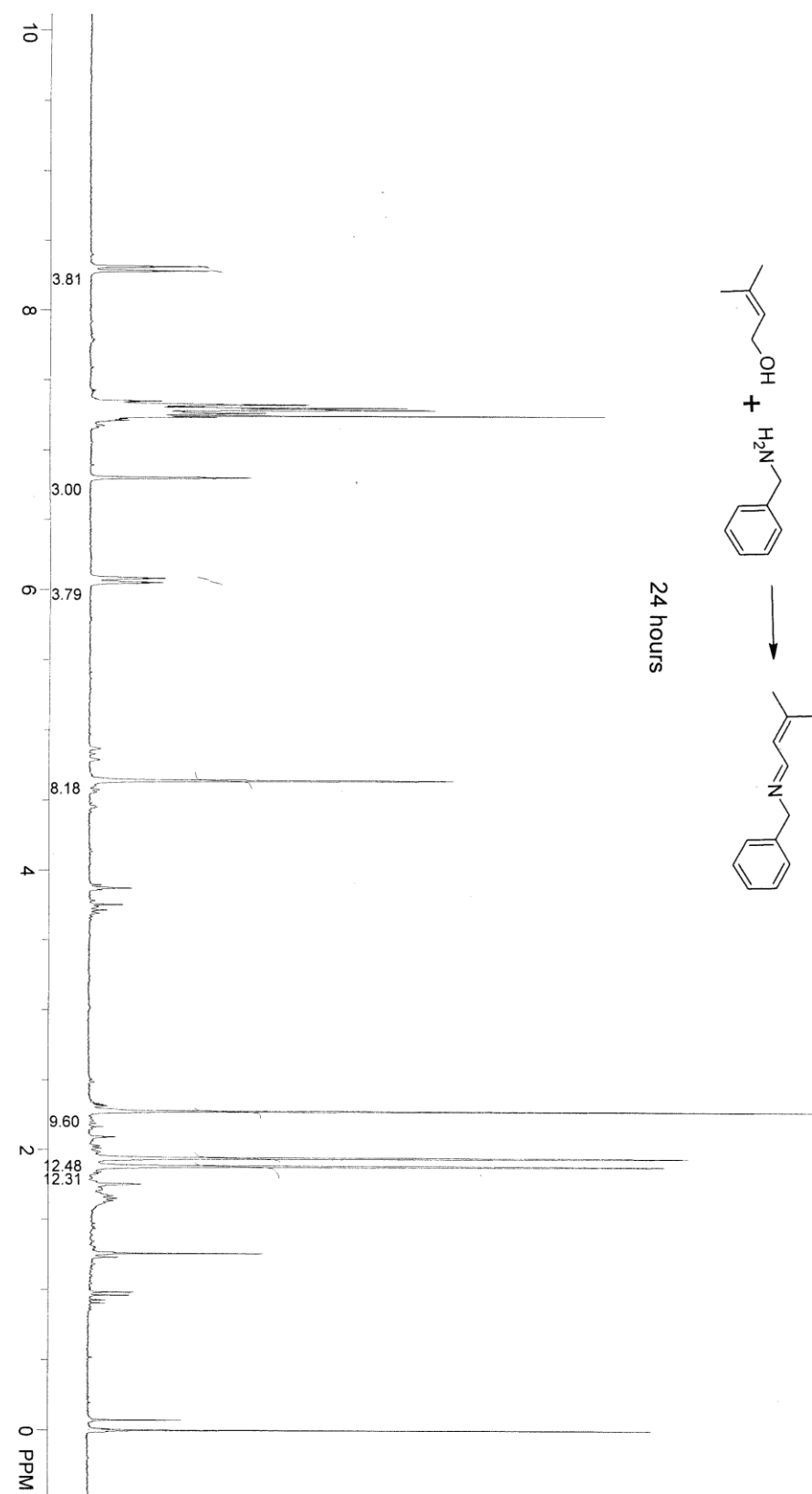
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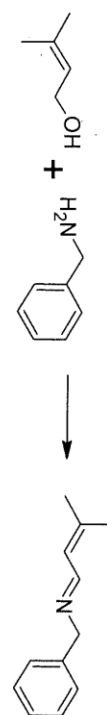
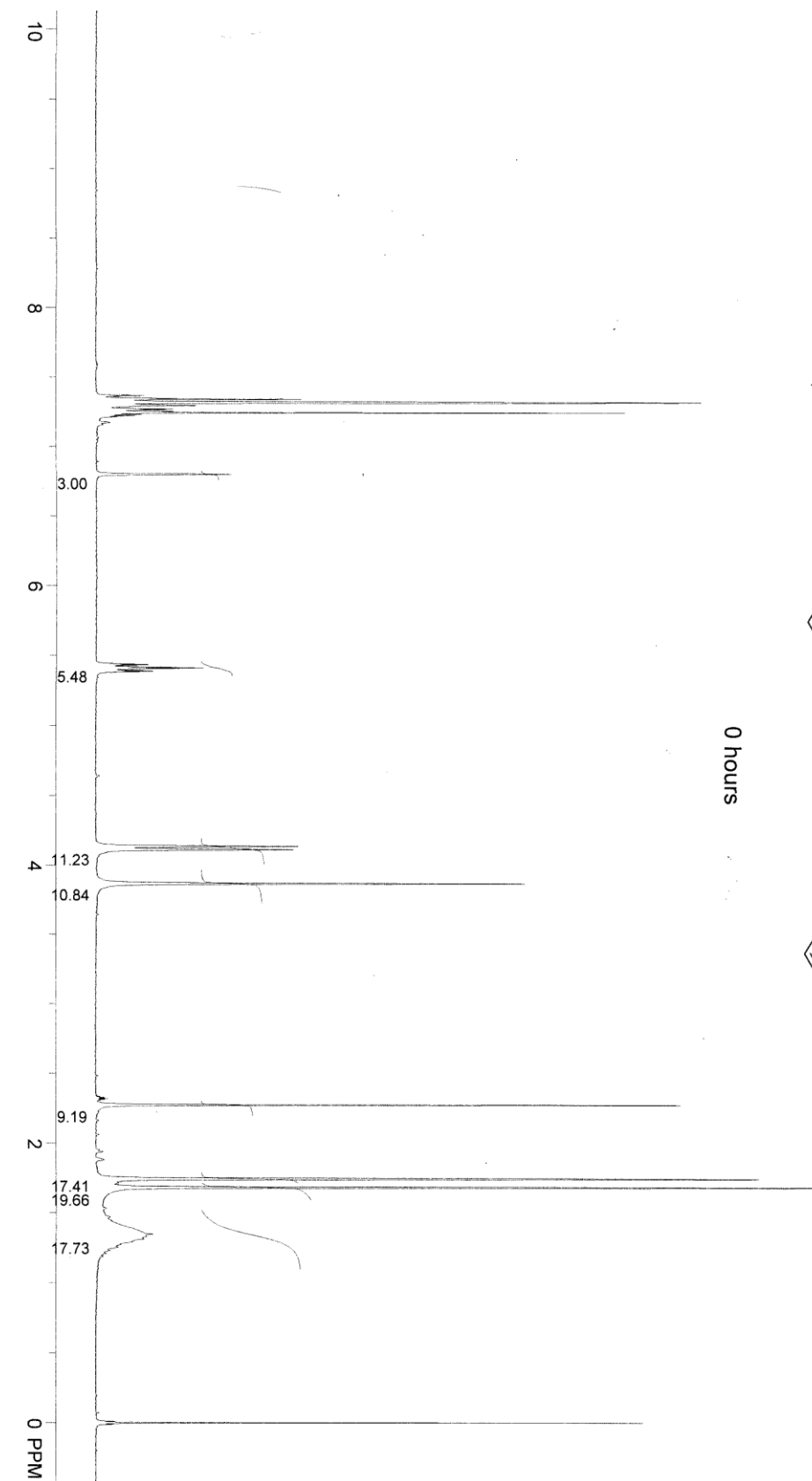
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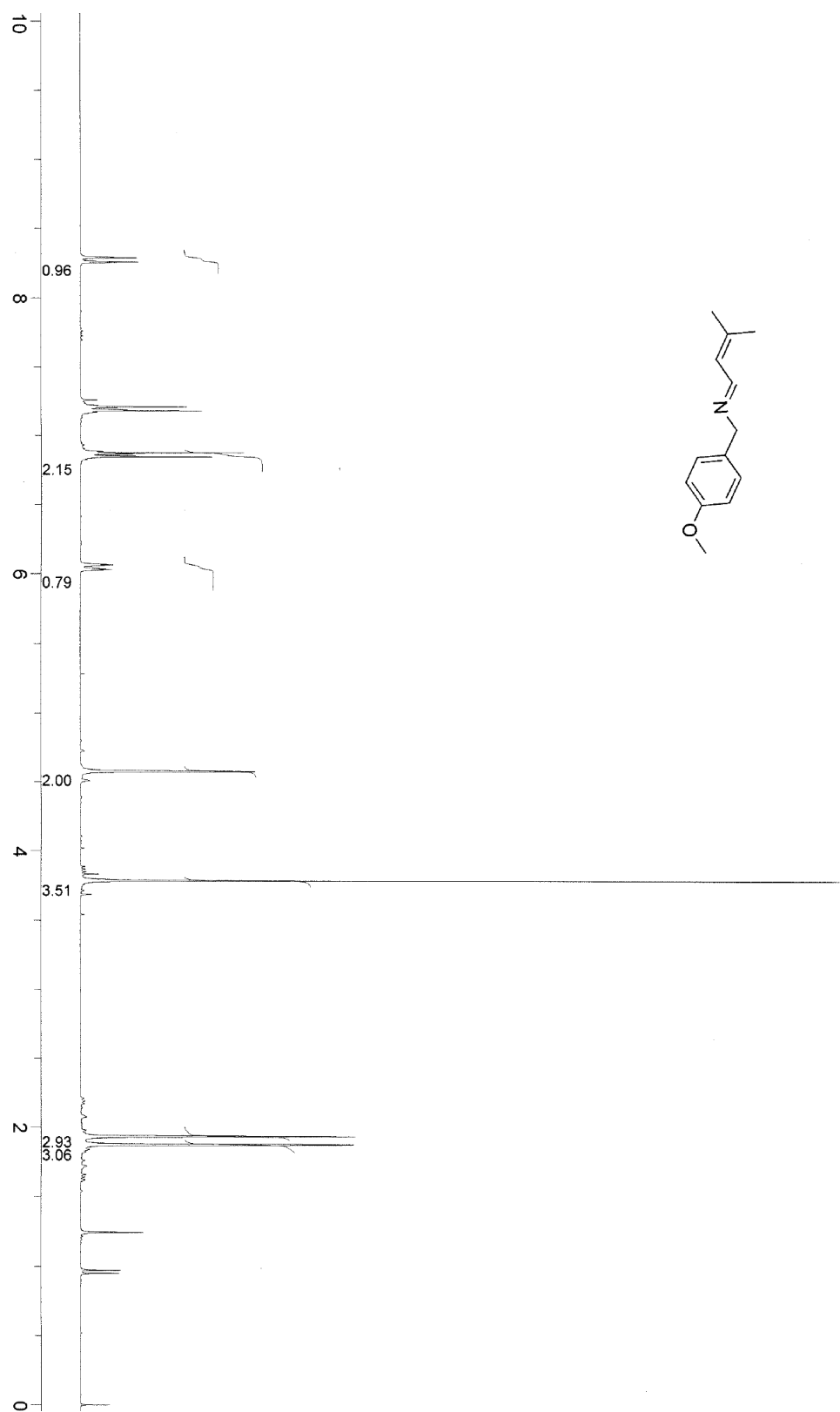
Reaction of 3a to 5 (Table 2, entry 1).



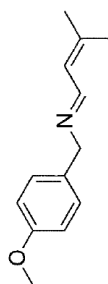
Reaction of 3a to 5 (Table 2, entry 1).



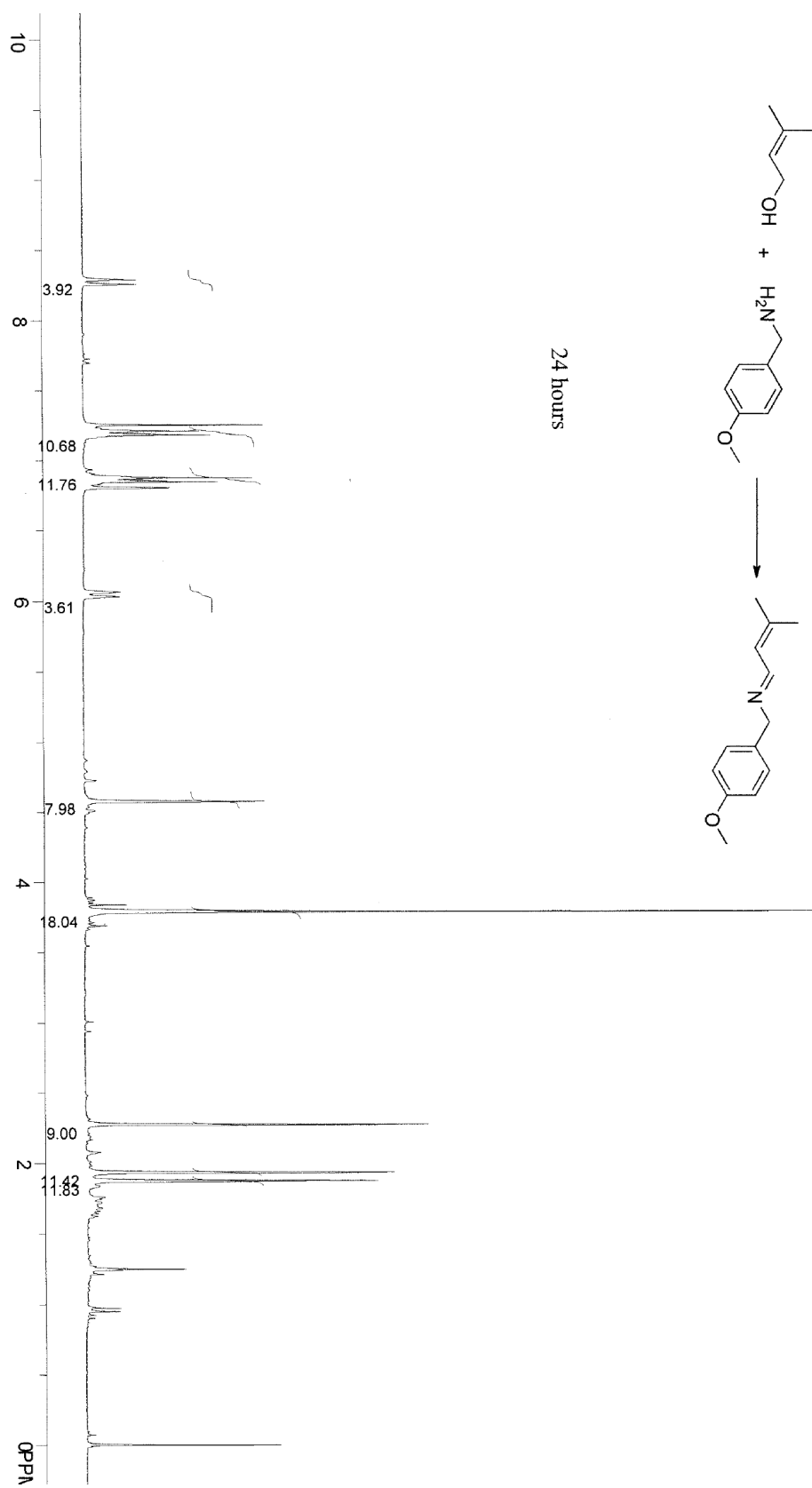
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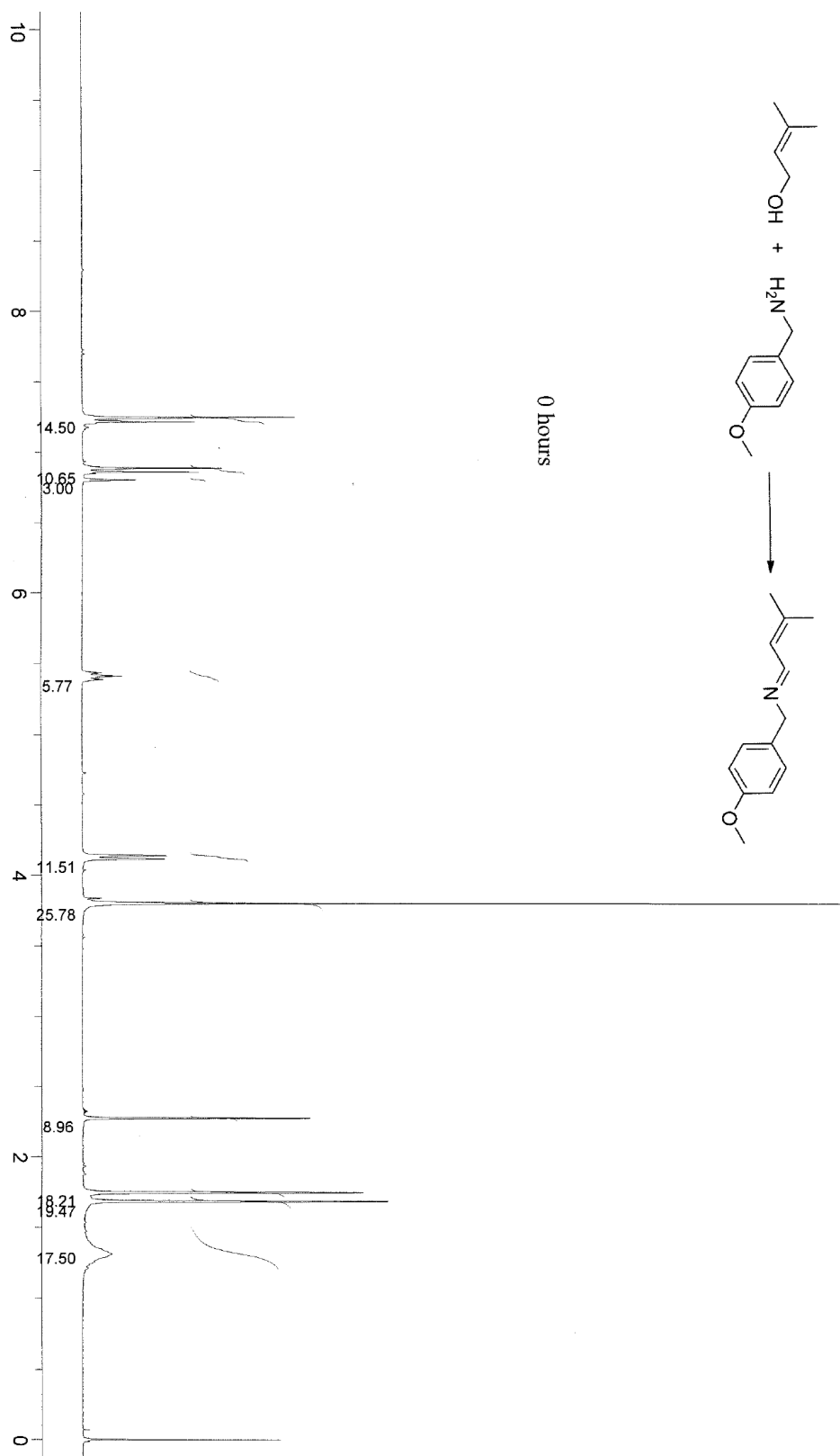
Compound 6.



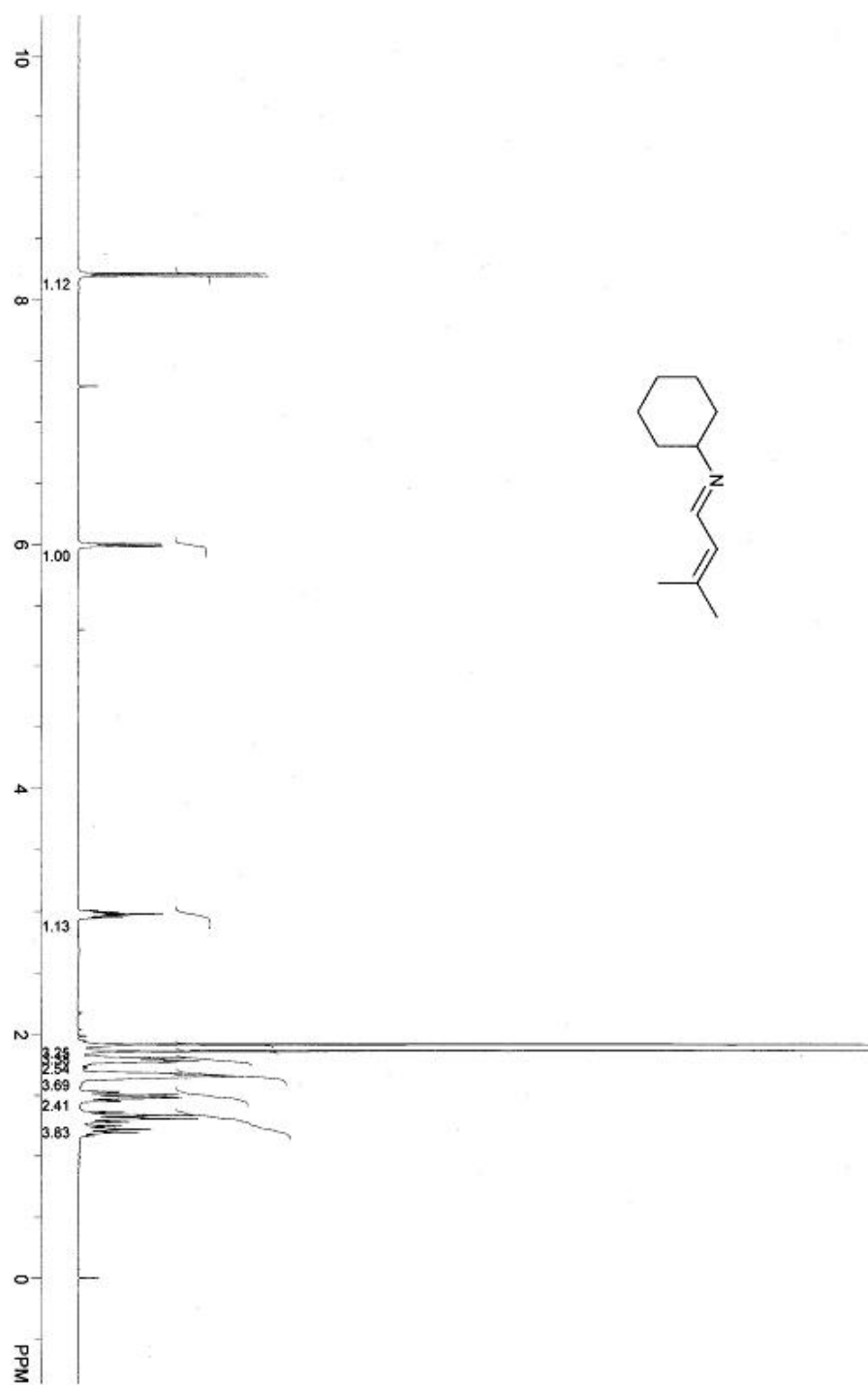
Reaction of 3a to 6 (Table 2, entry 2).



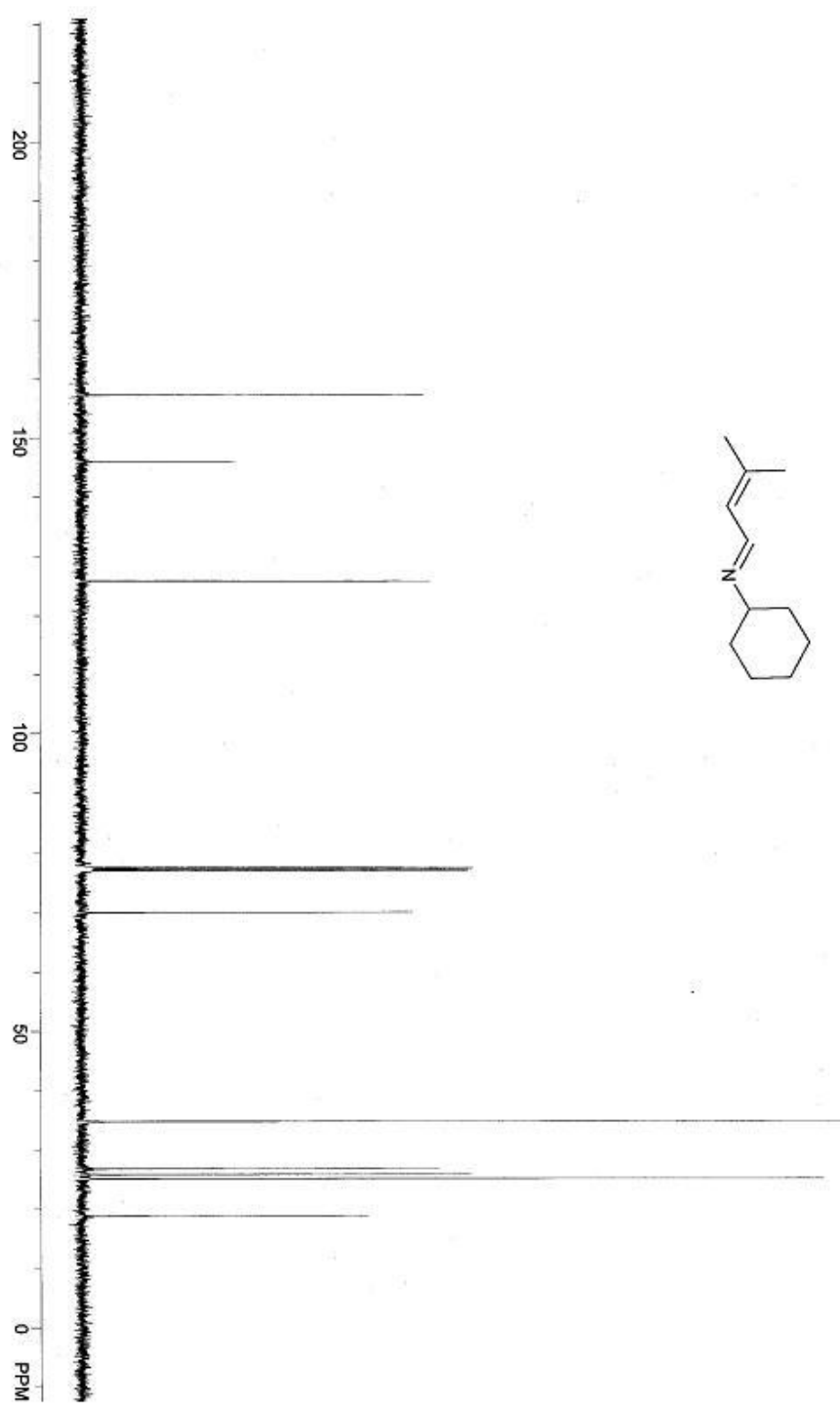
Reaction of 3a to 6 (Table 2, entry 2).



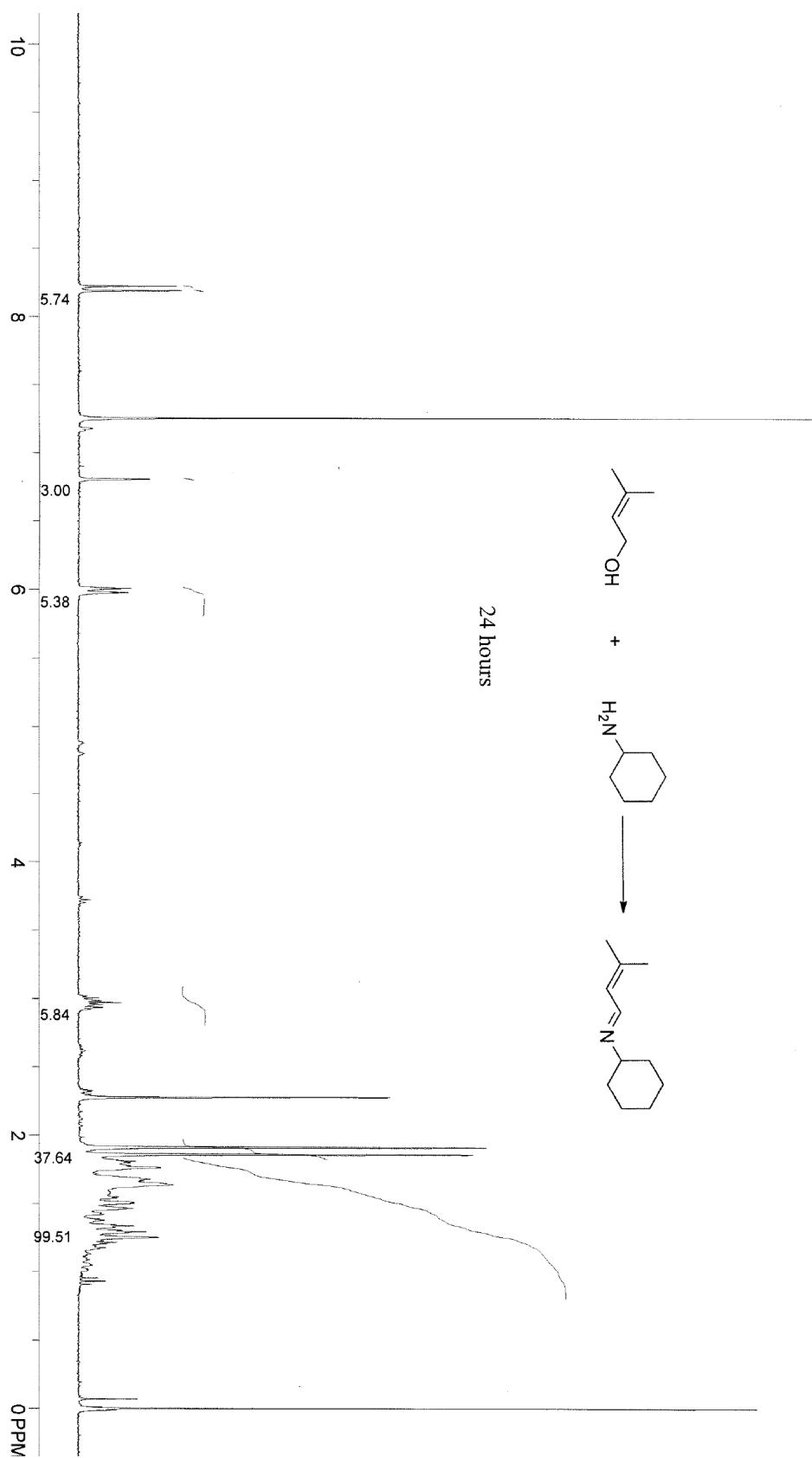
Compound 7.



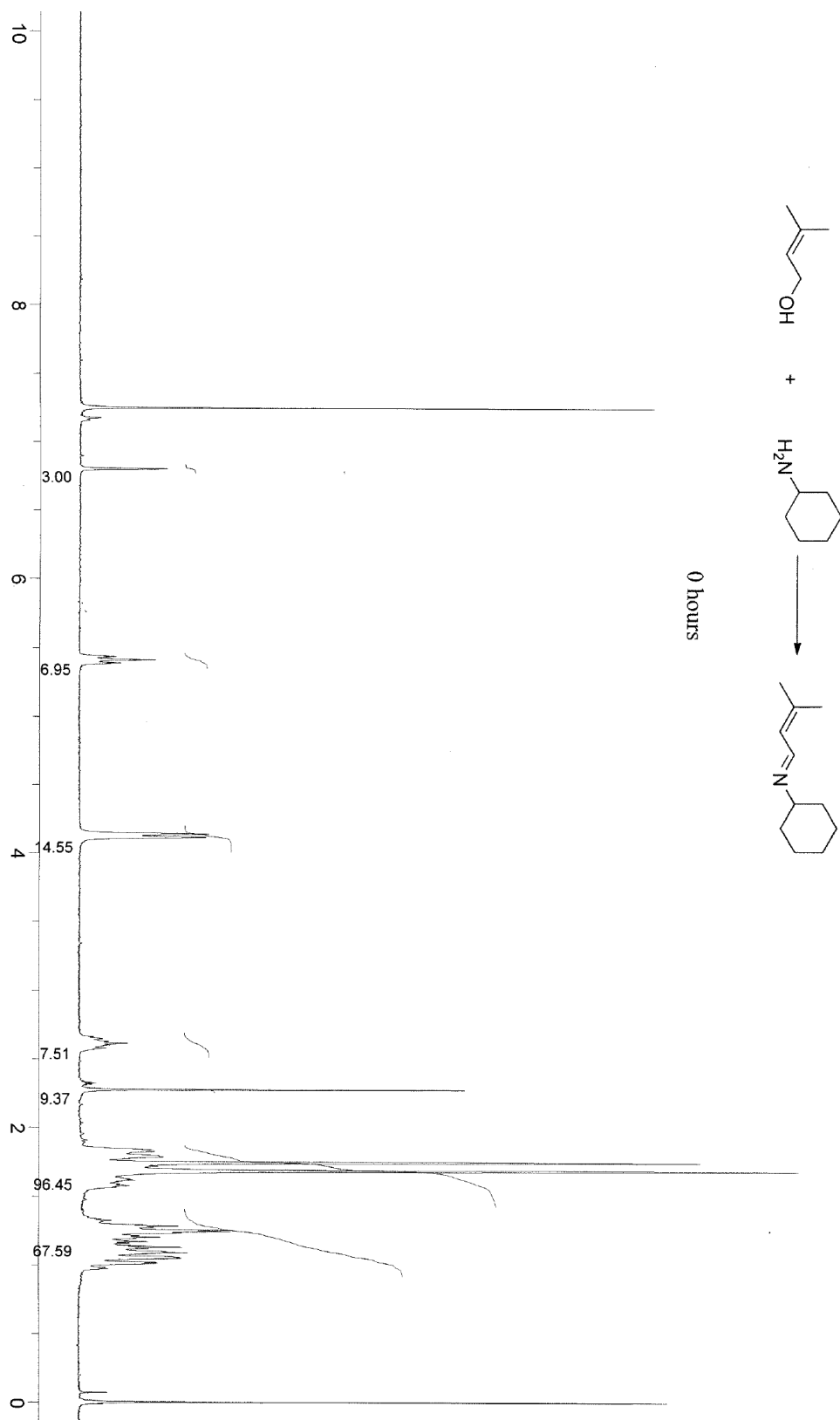
Compound 7.



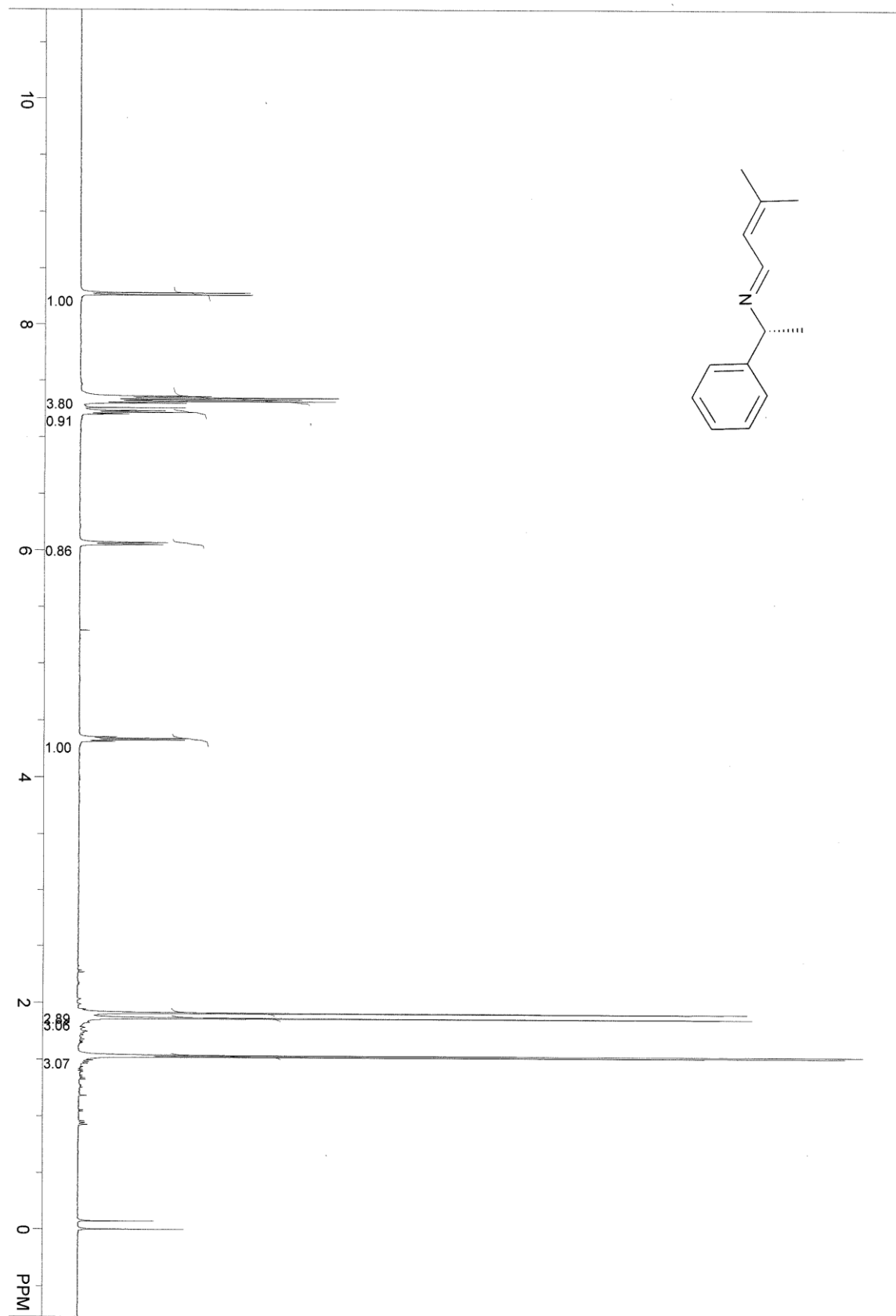
Reaction of 3a to 7 (Table 2, entry 3).



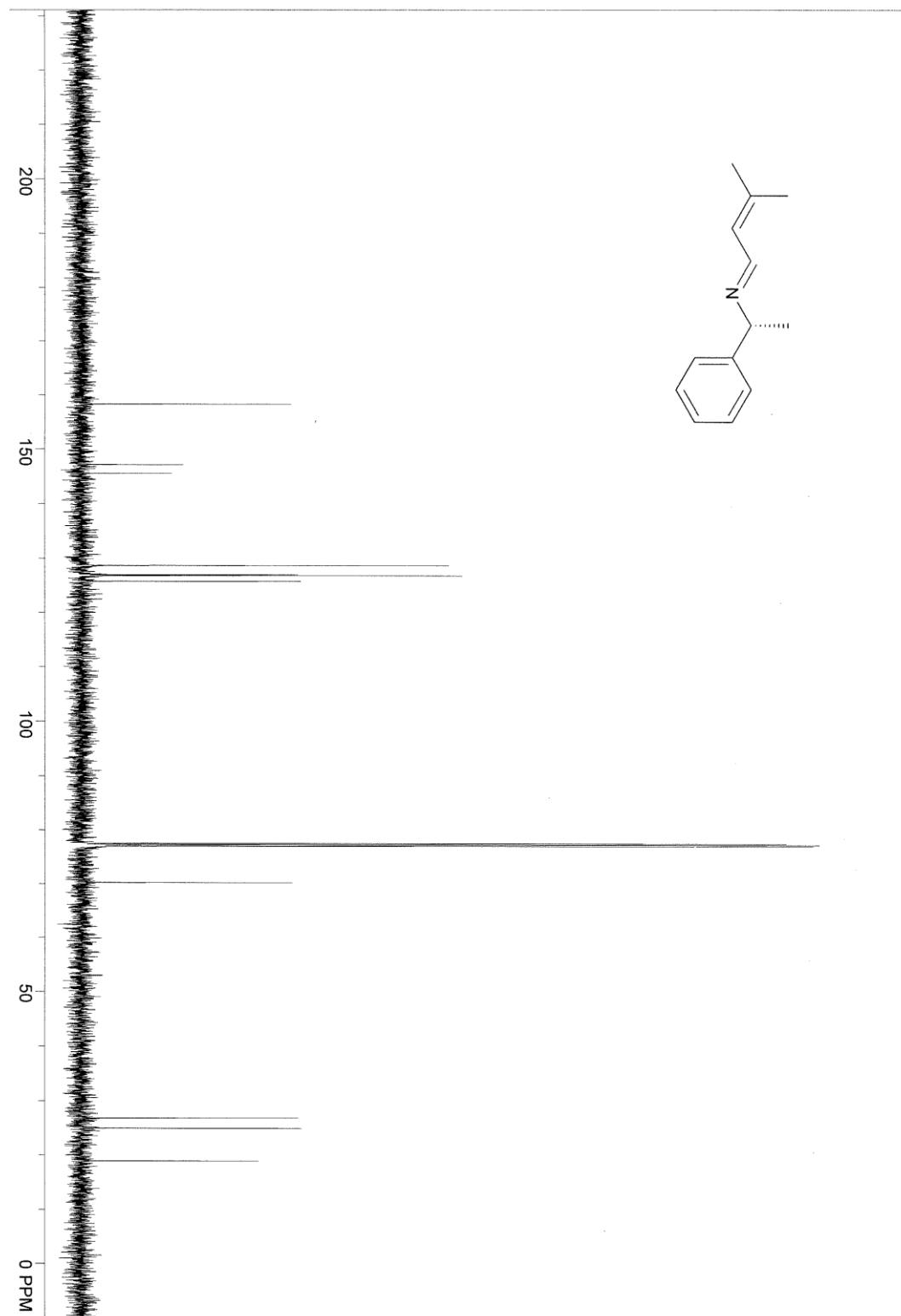
Reaction of 3a to 7 (Table 2, entry 3).



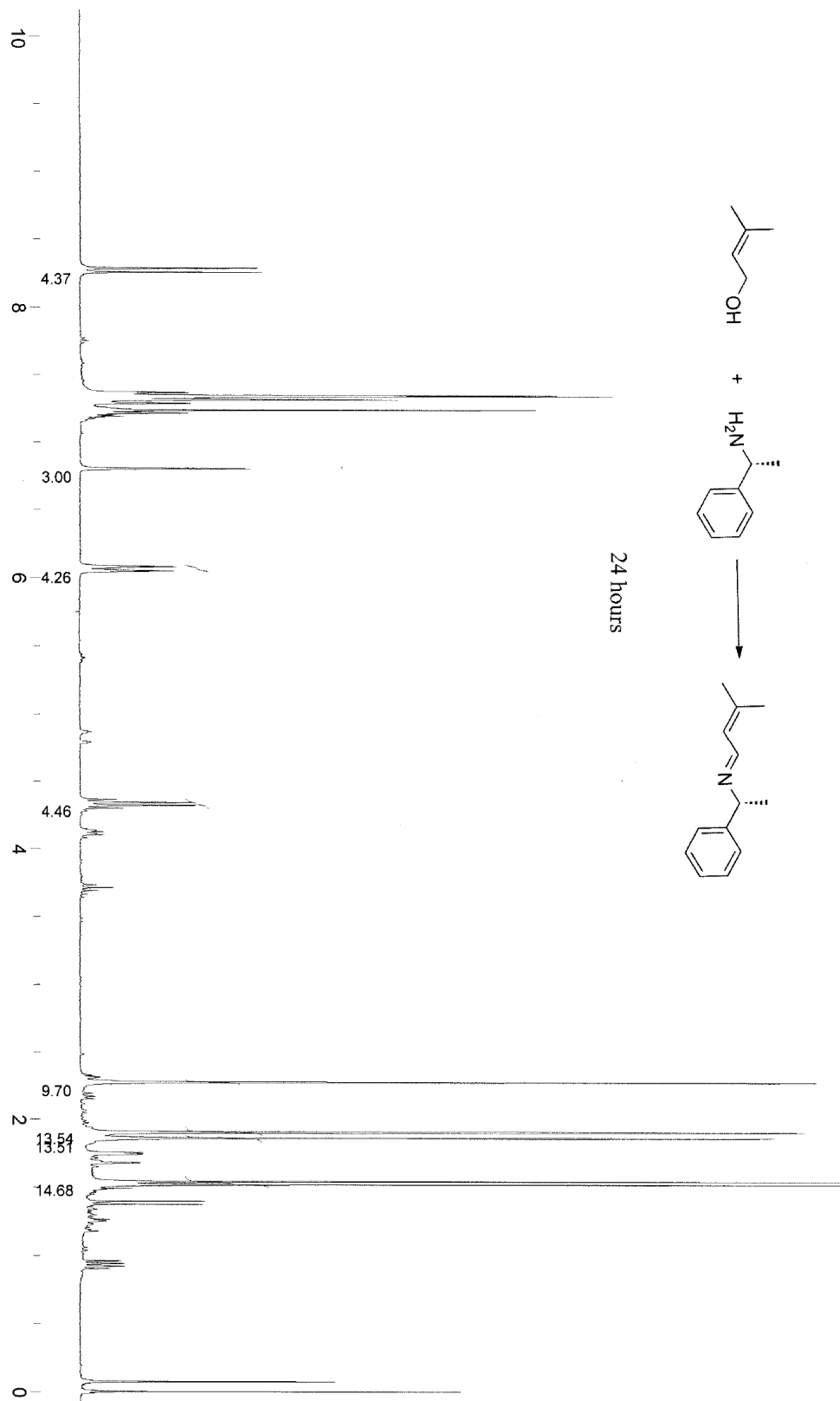
Compound 8.



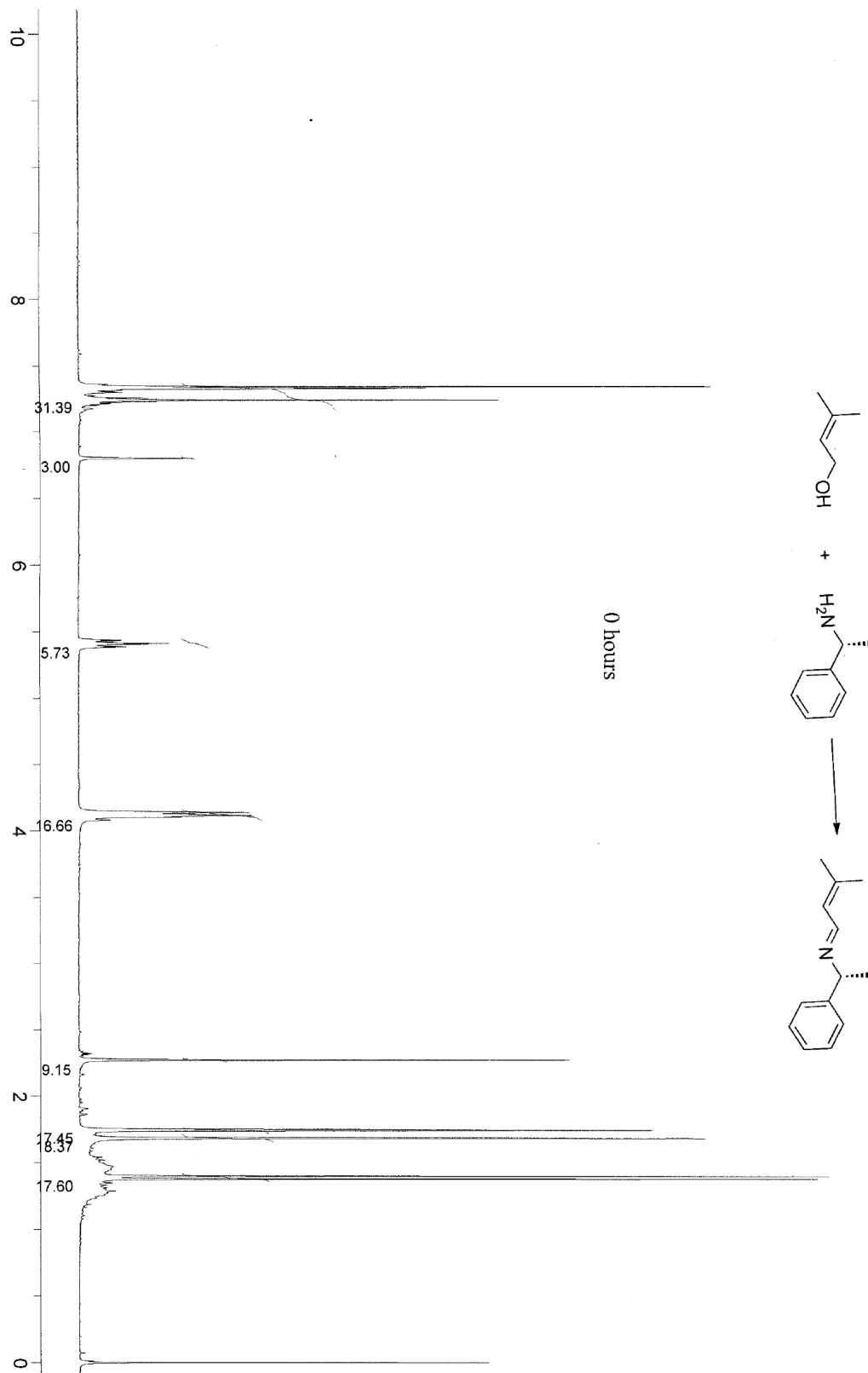
Compound 8.



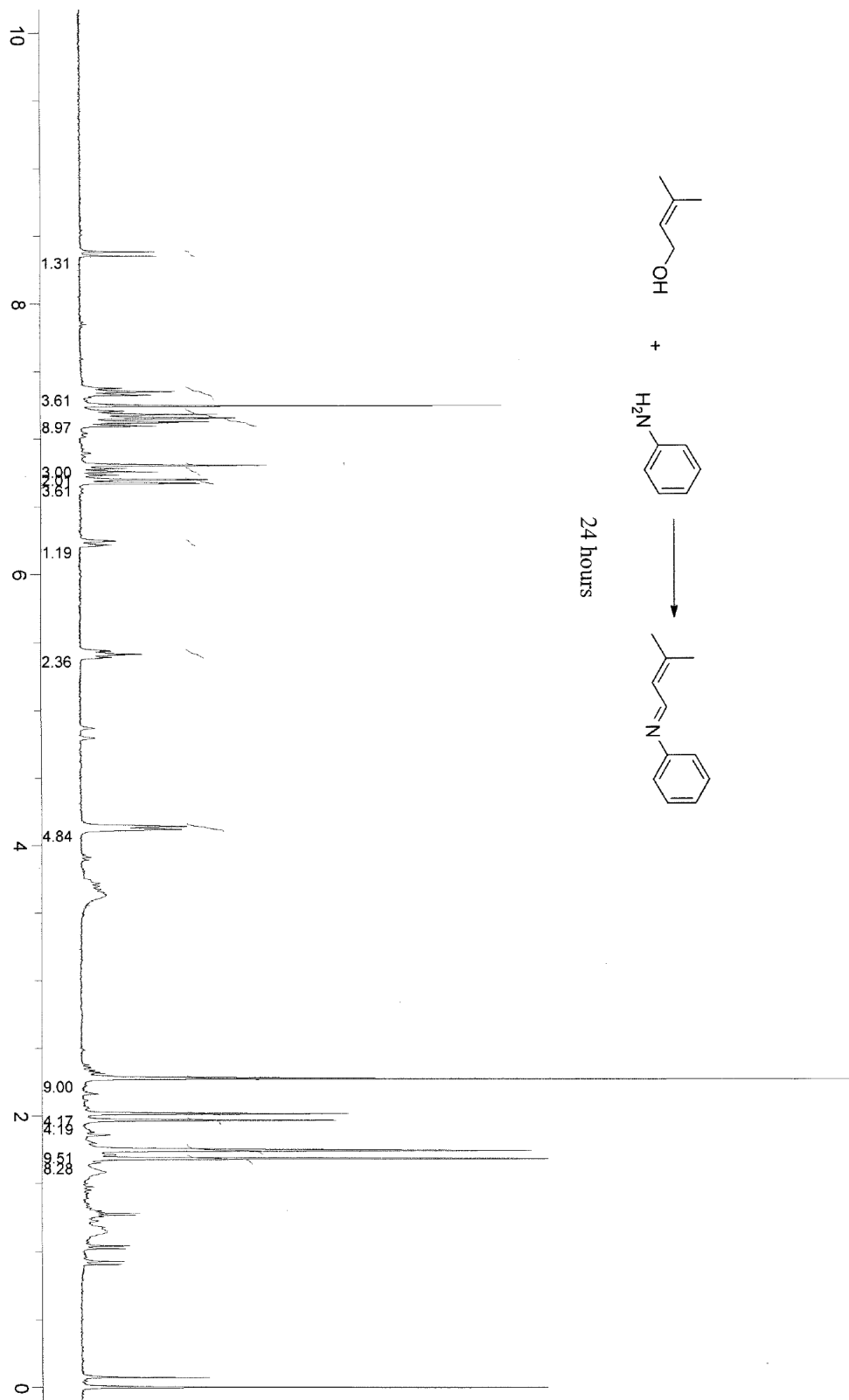
Reaction of 3a to 8 (Table 2, entry 4).



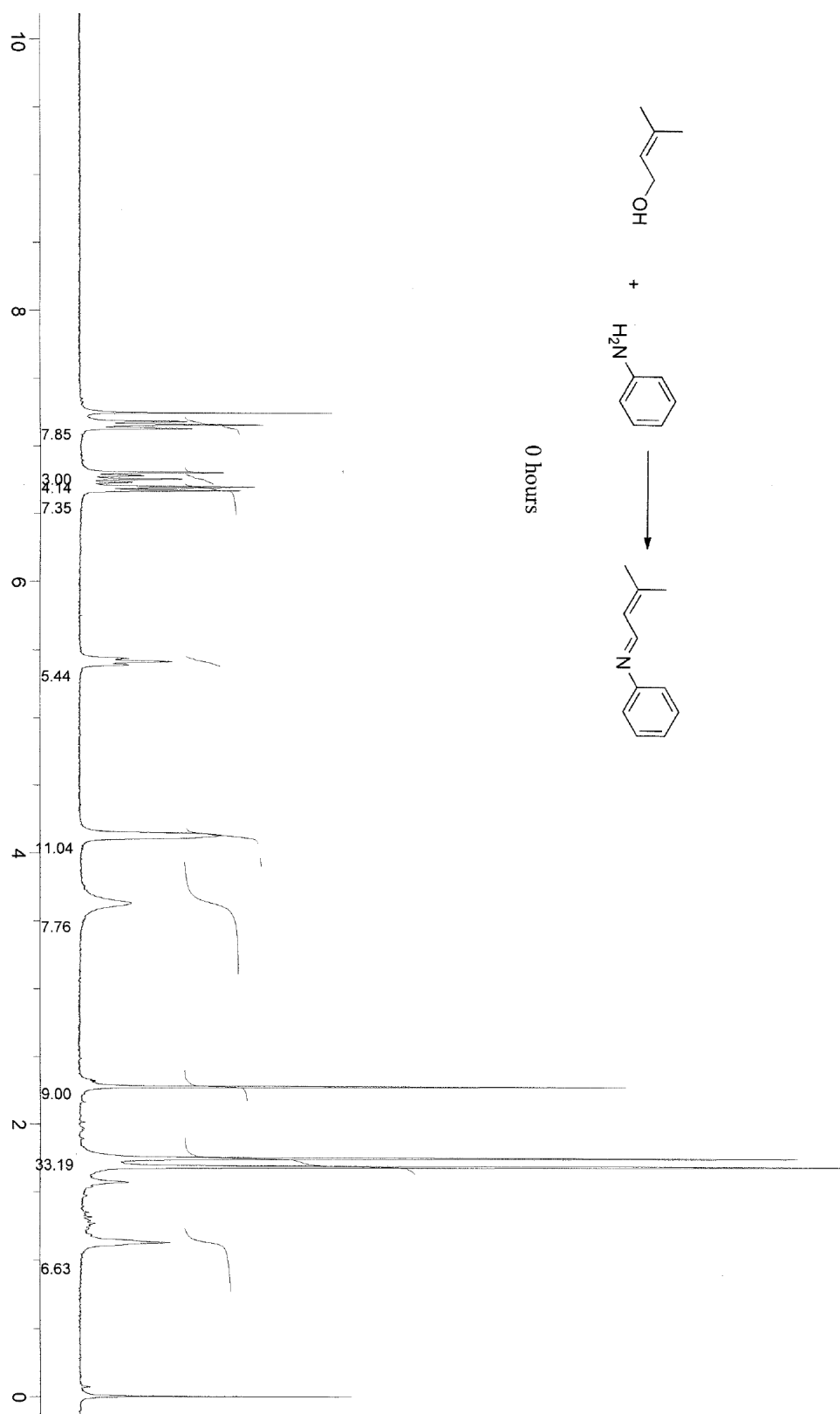
Reaction of 3a to 8 (Table 2, entry 4).



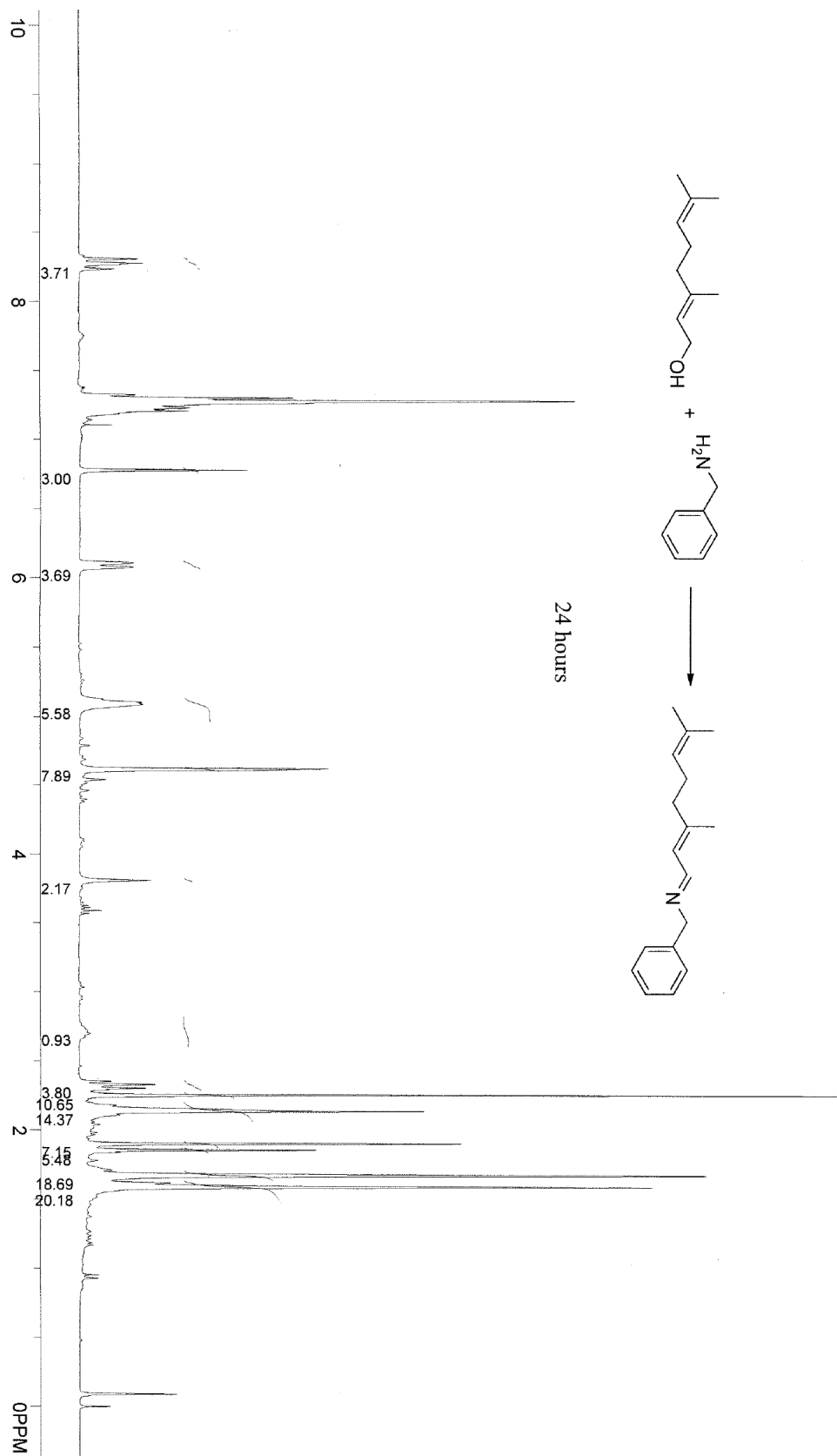
Reaction of 3a to 9 (Table 2, entry 5).



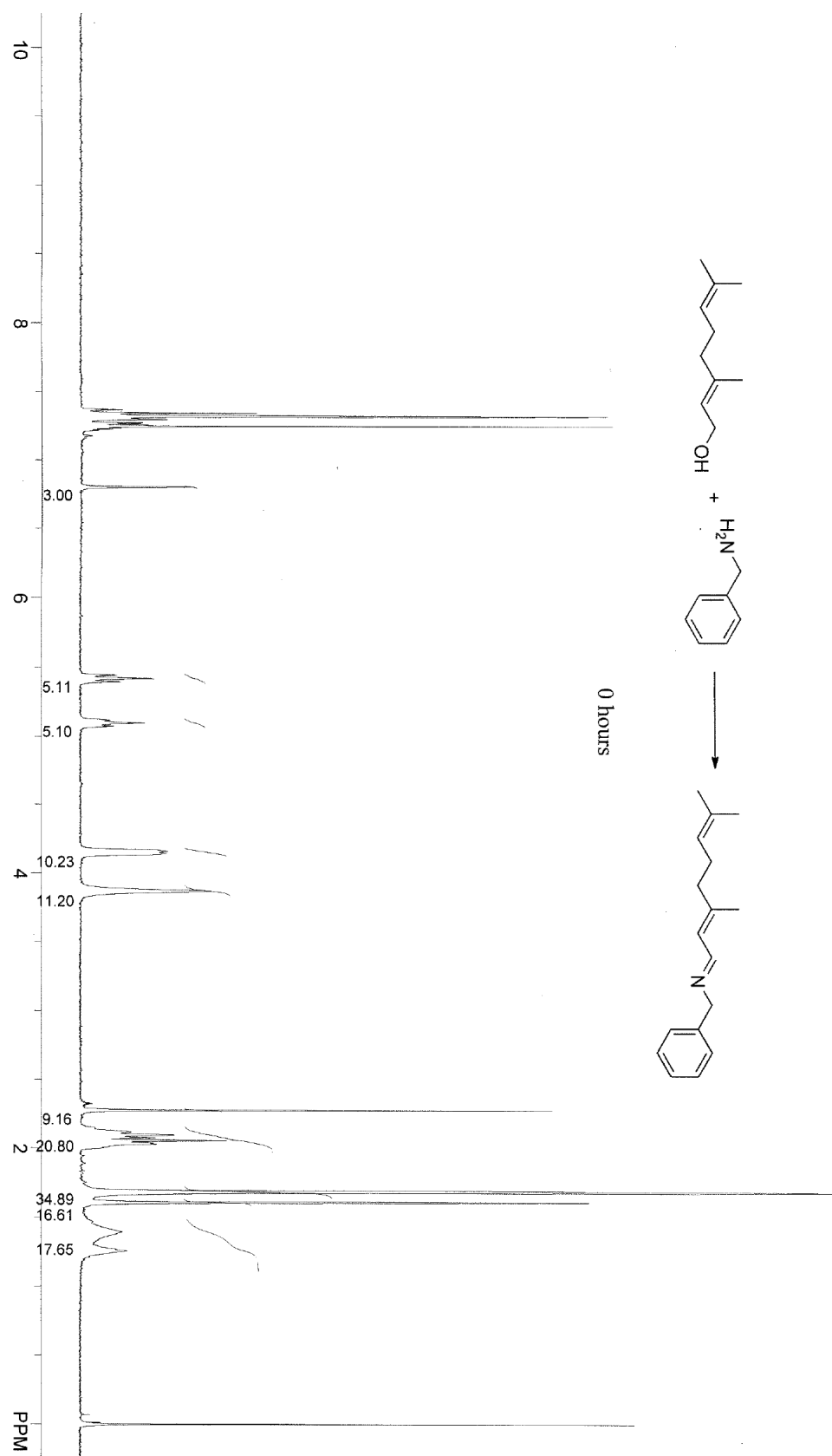
Reaction of 3a to 9 (Table 2, entry 5).



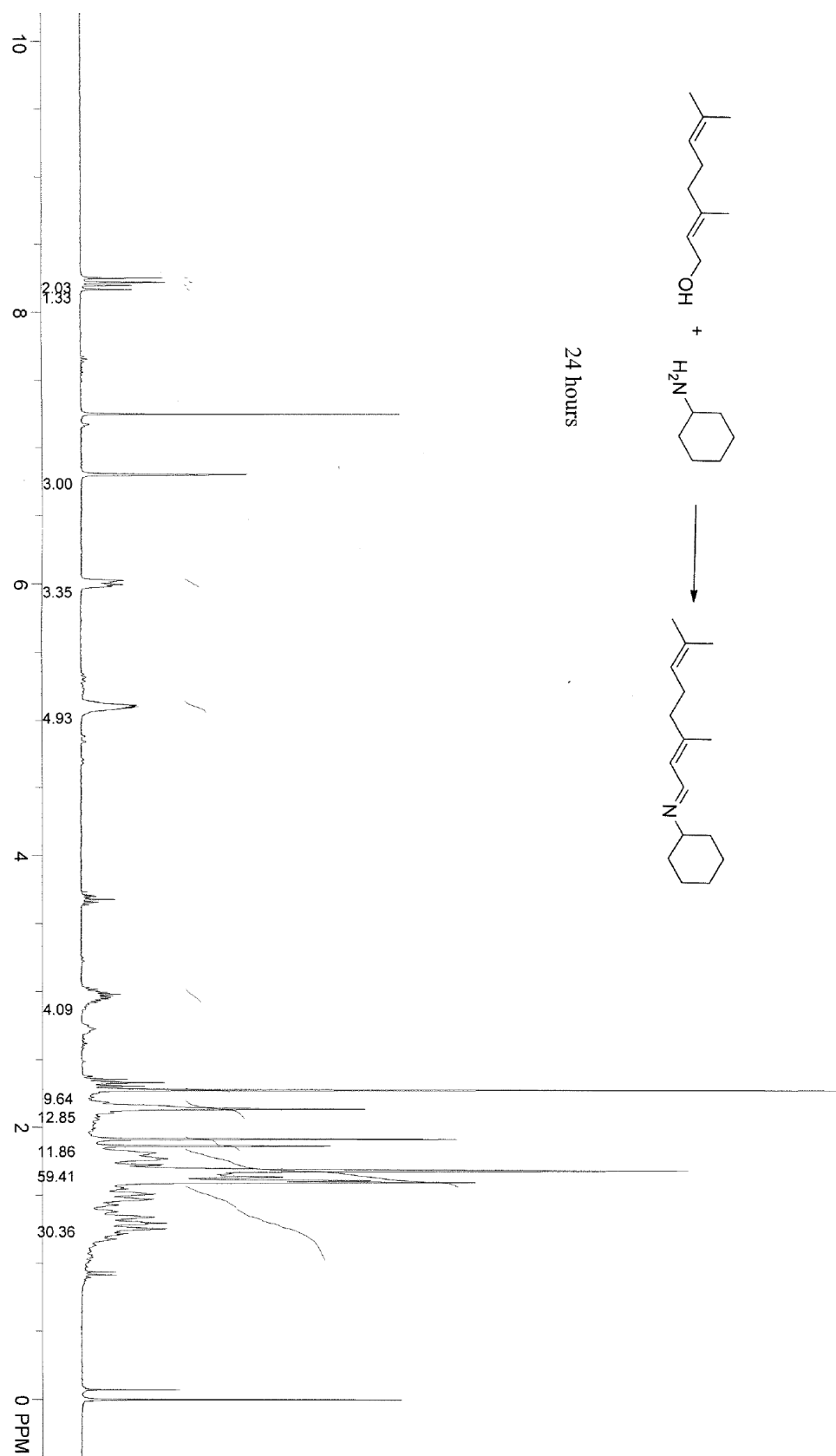
Reaction of 3b to 10 (Table 2, entry 6).



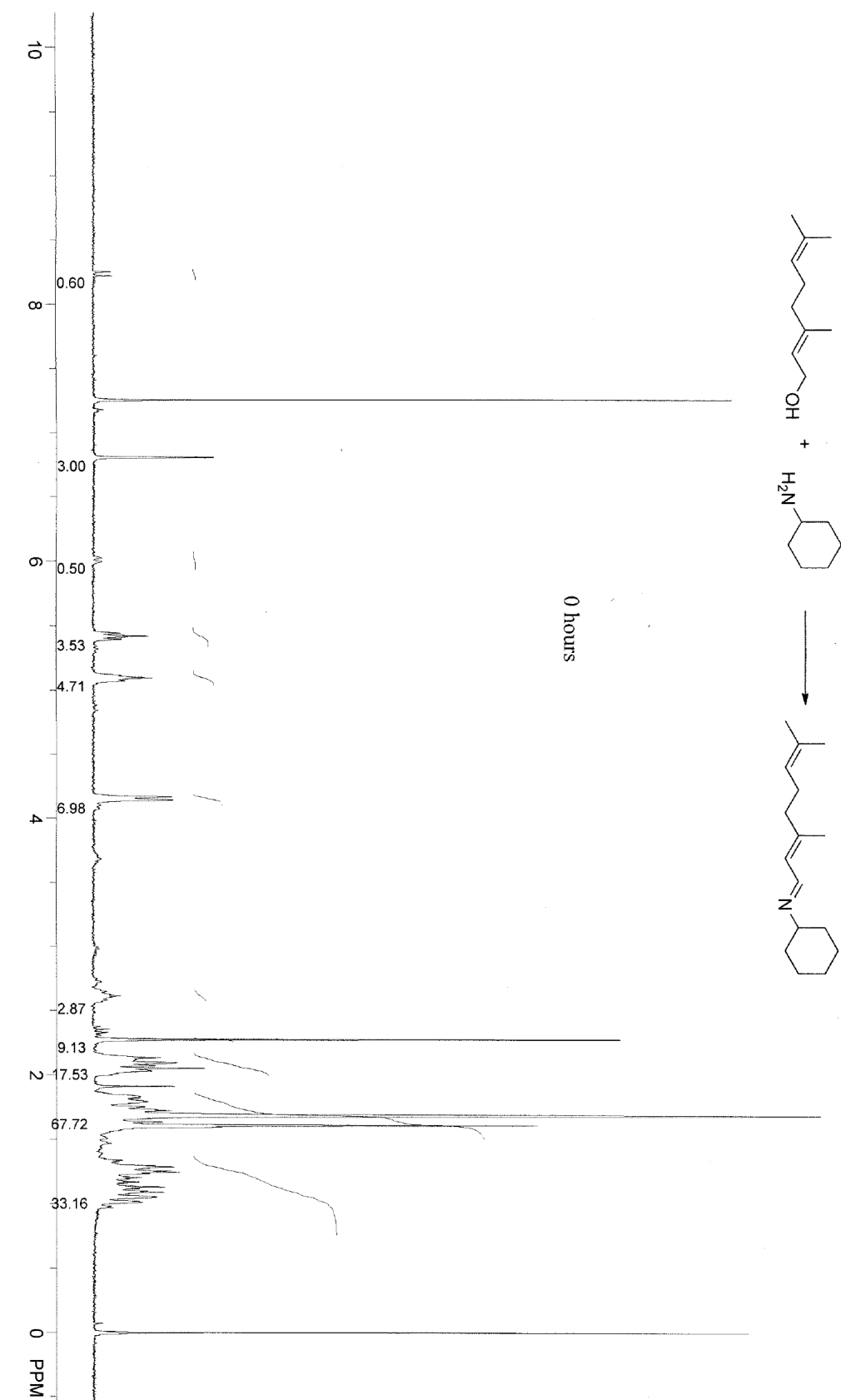
Reaction of 3b to 10 (Table 2, entry 6).



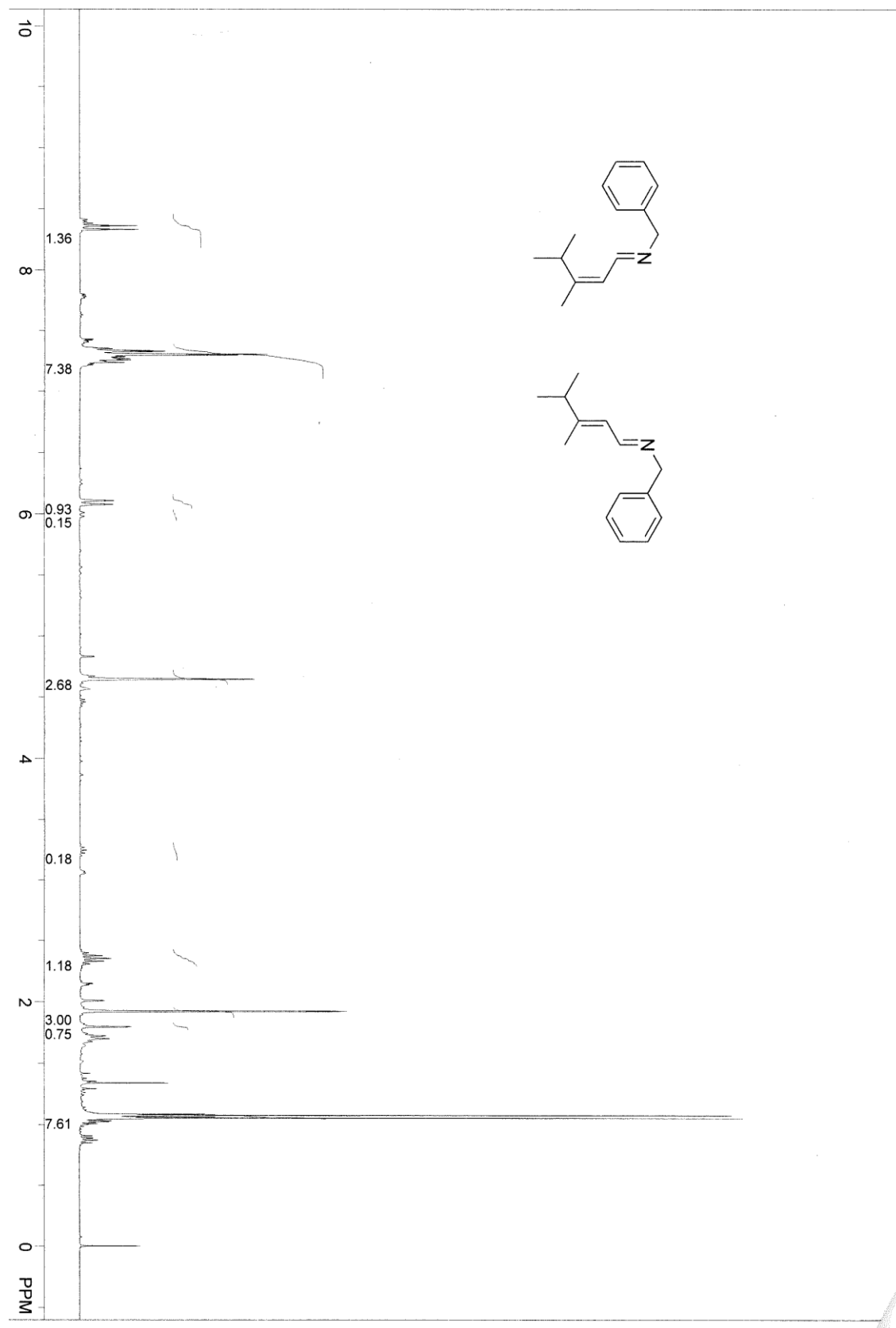
Reaction of 3b to 11 (Table 2, entry 7).



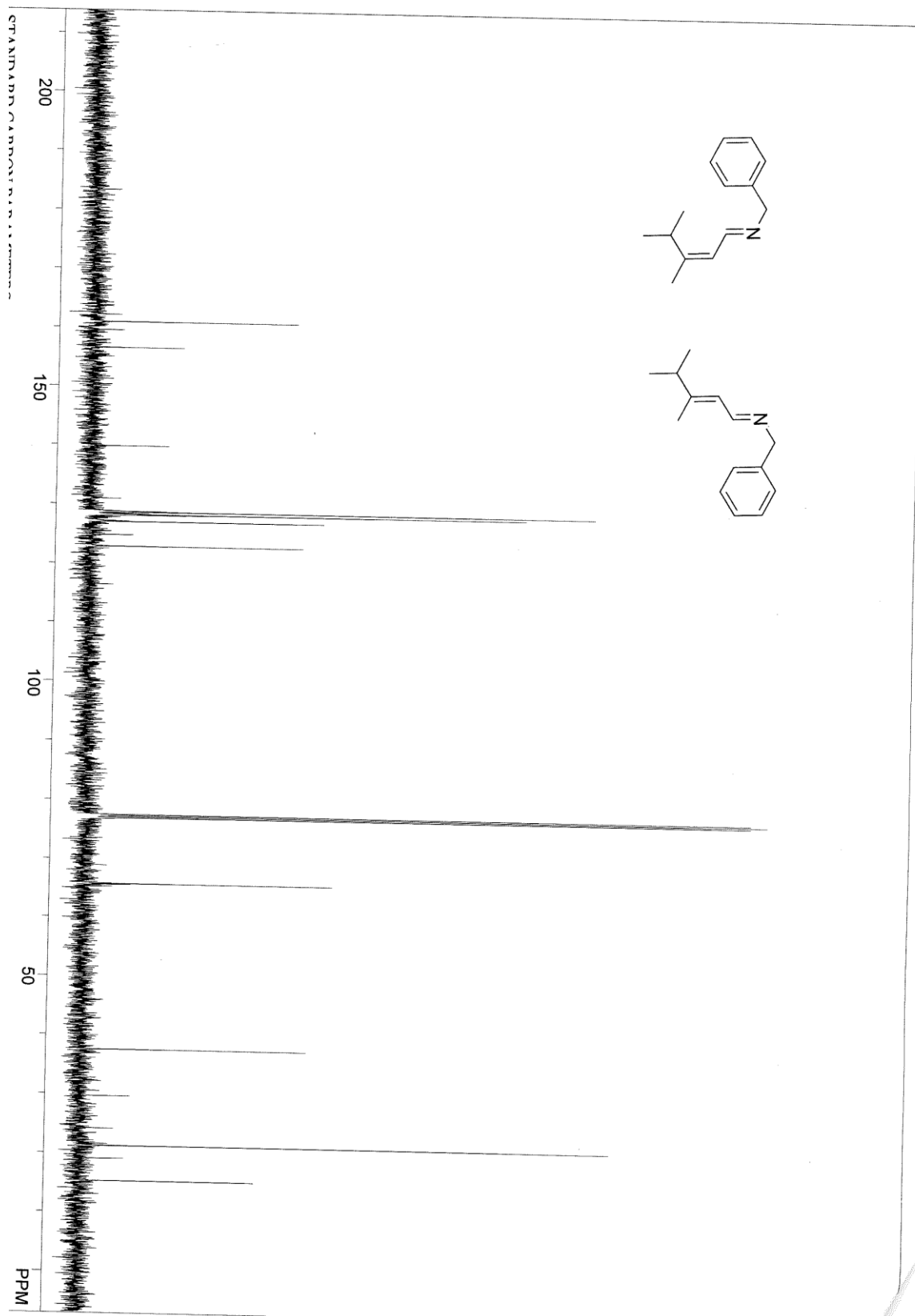
Reaction of 3b to 11 (Table 2, entry 7).



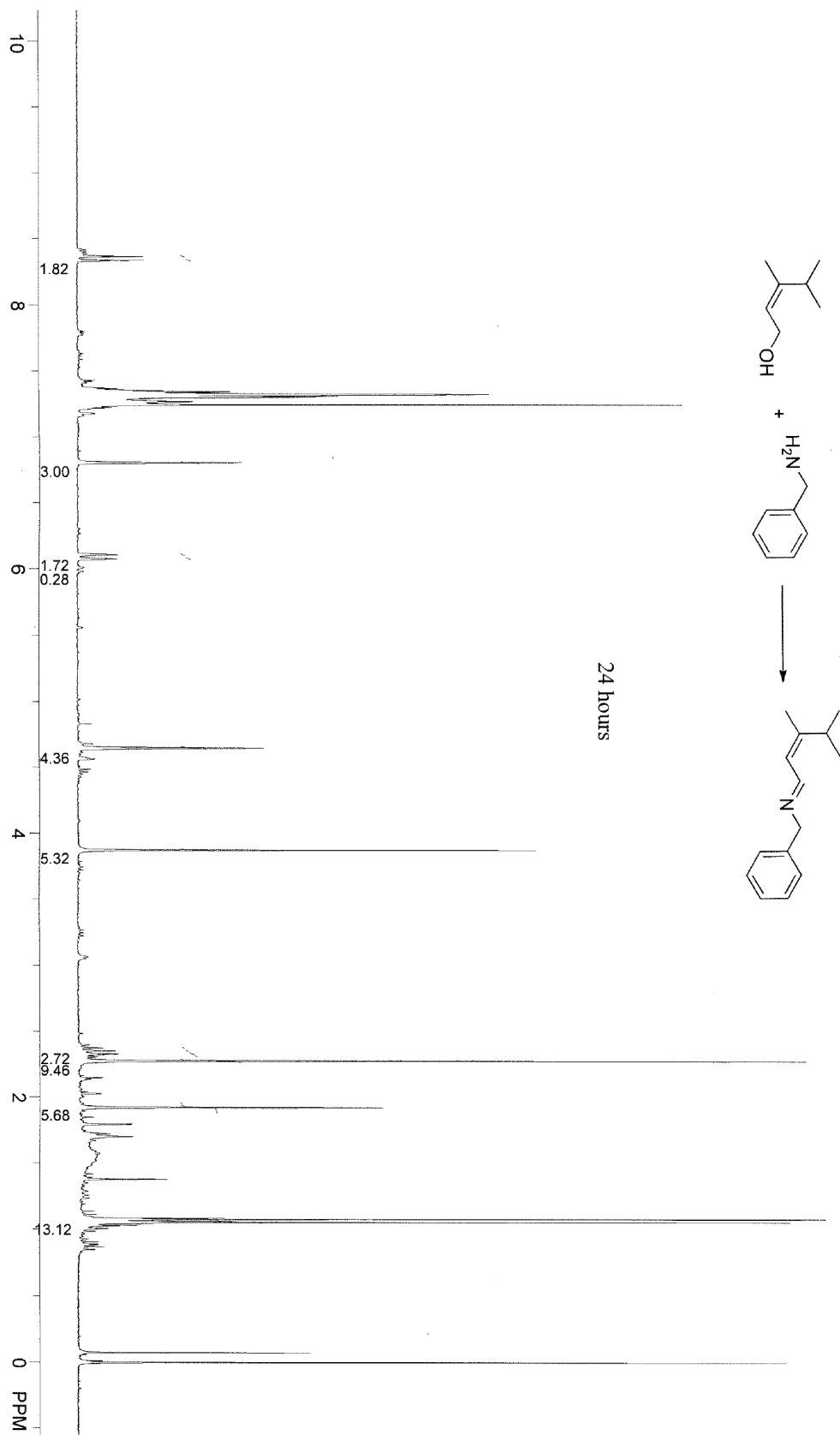
Compound 12.



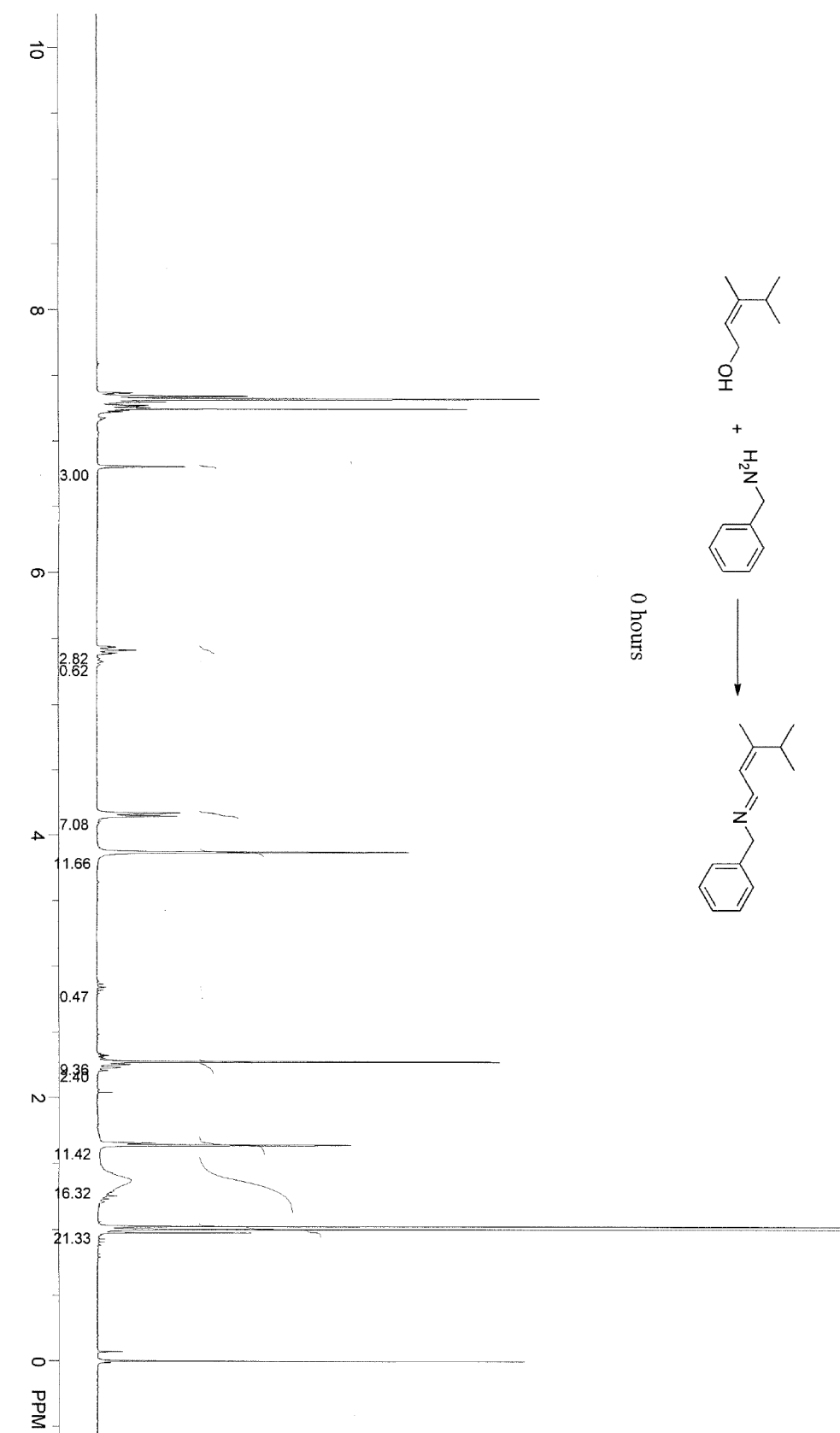
Compound 12.



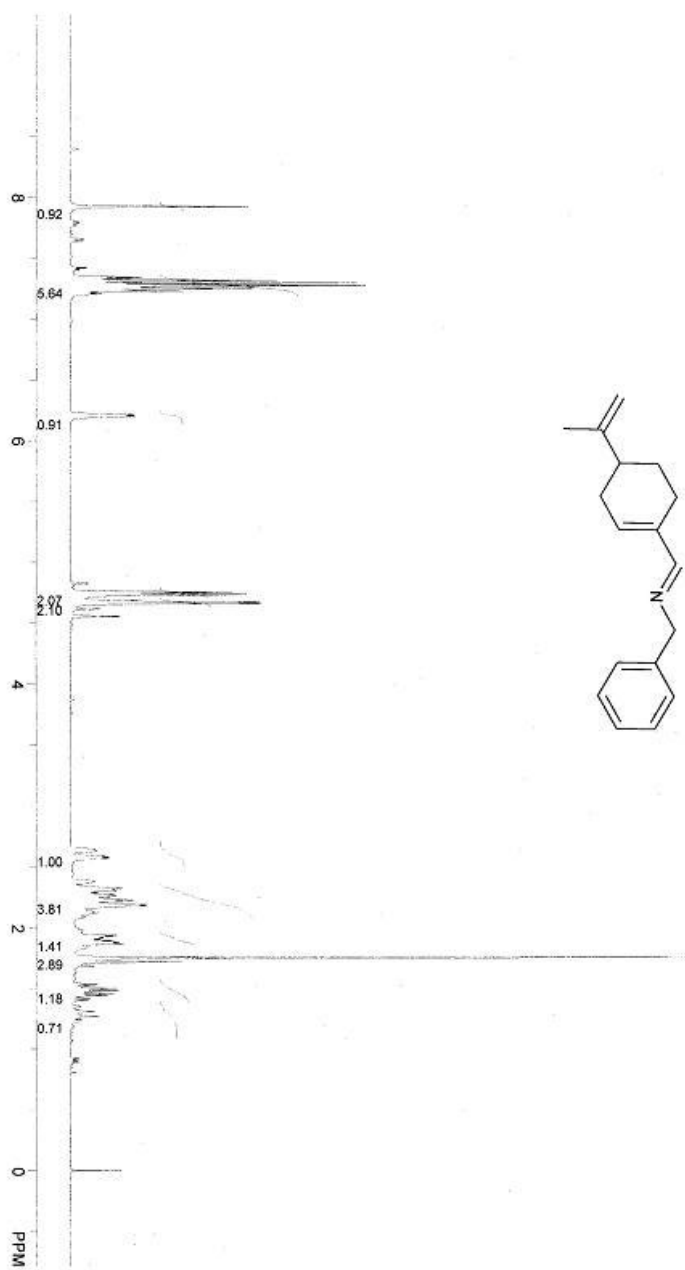
Reaction of 3c to 12 (Table 2, entry 8).



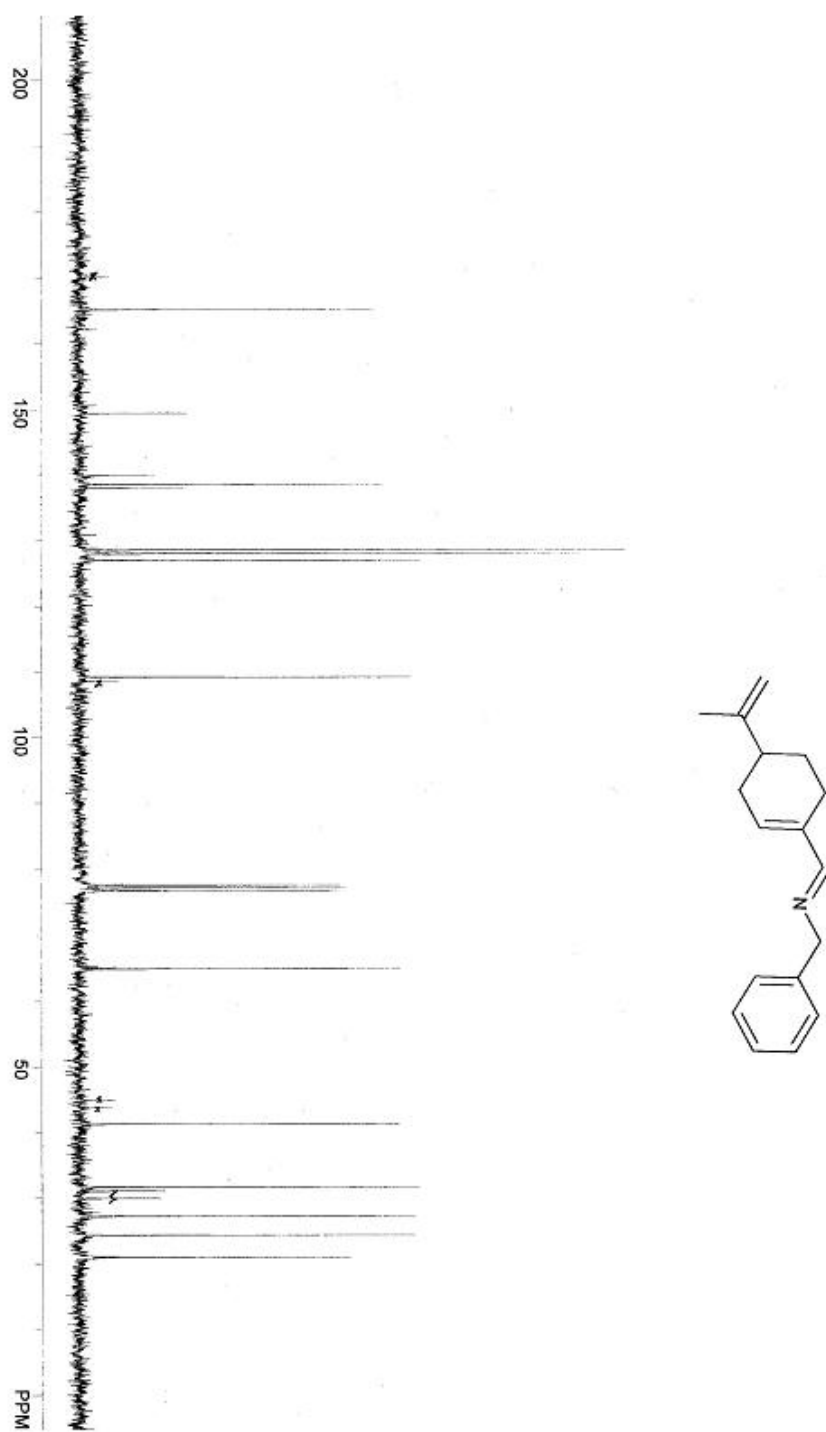
Reaction of 3c to 12 (Table 2, entry 8).



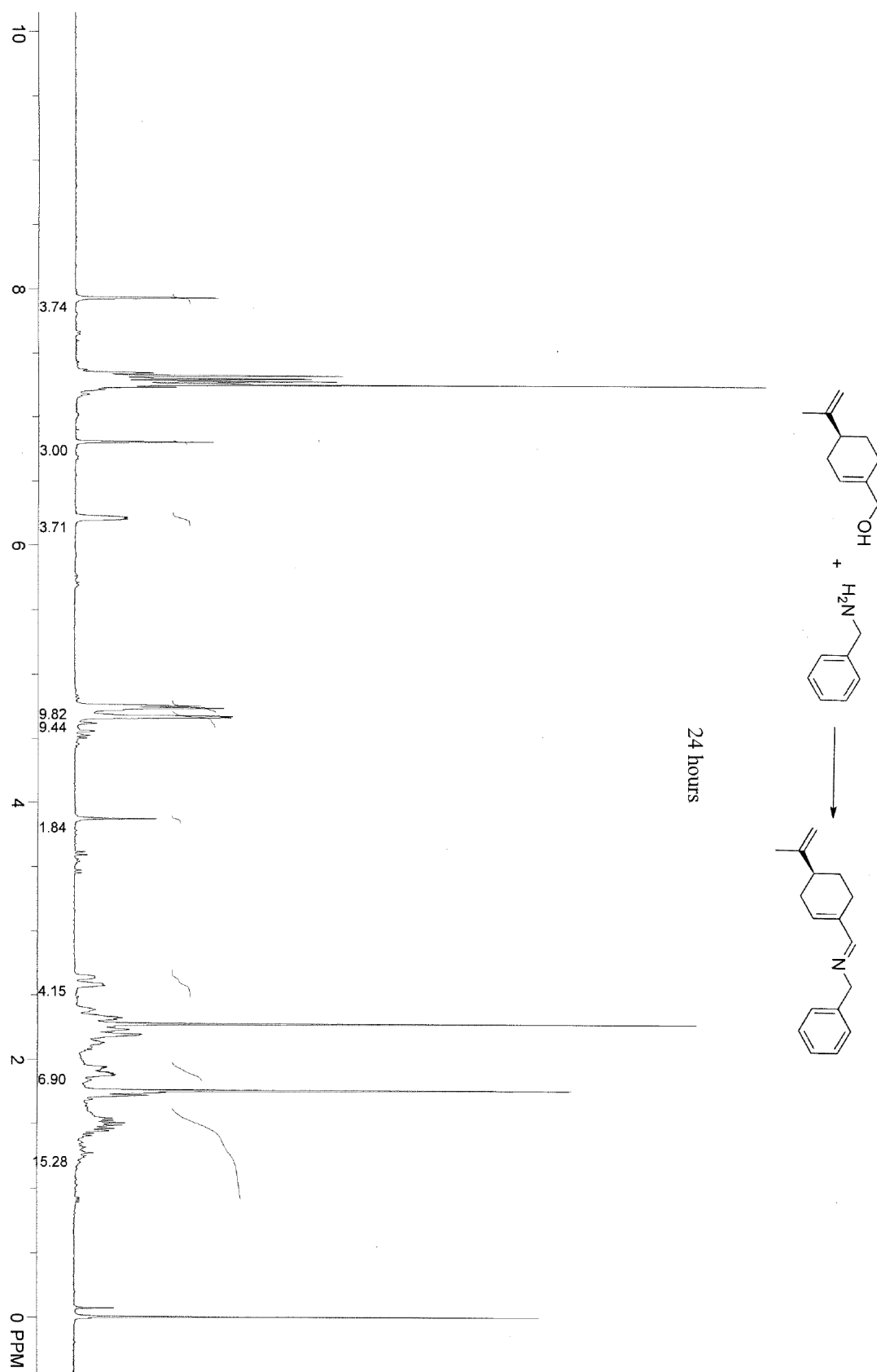
Compound 13.



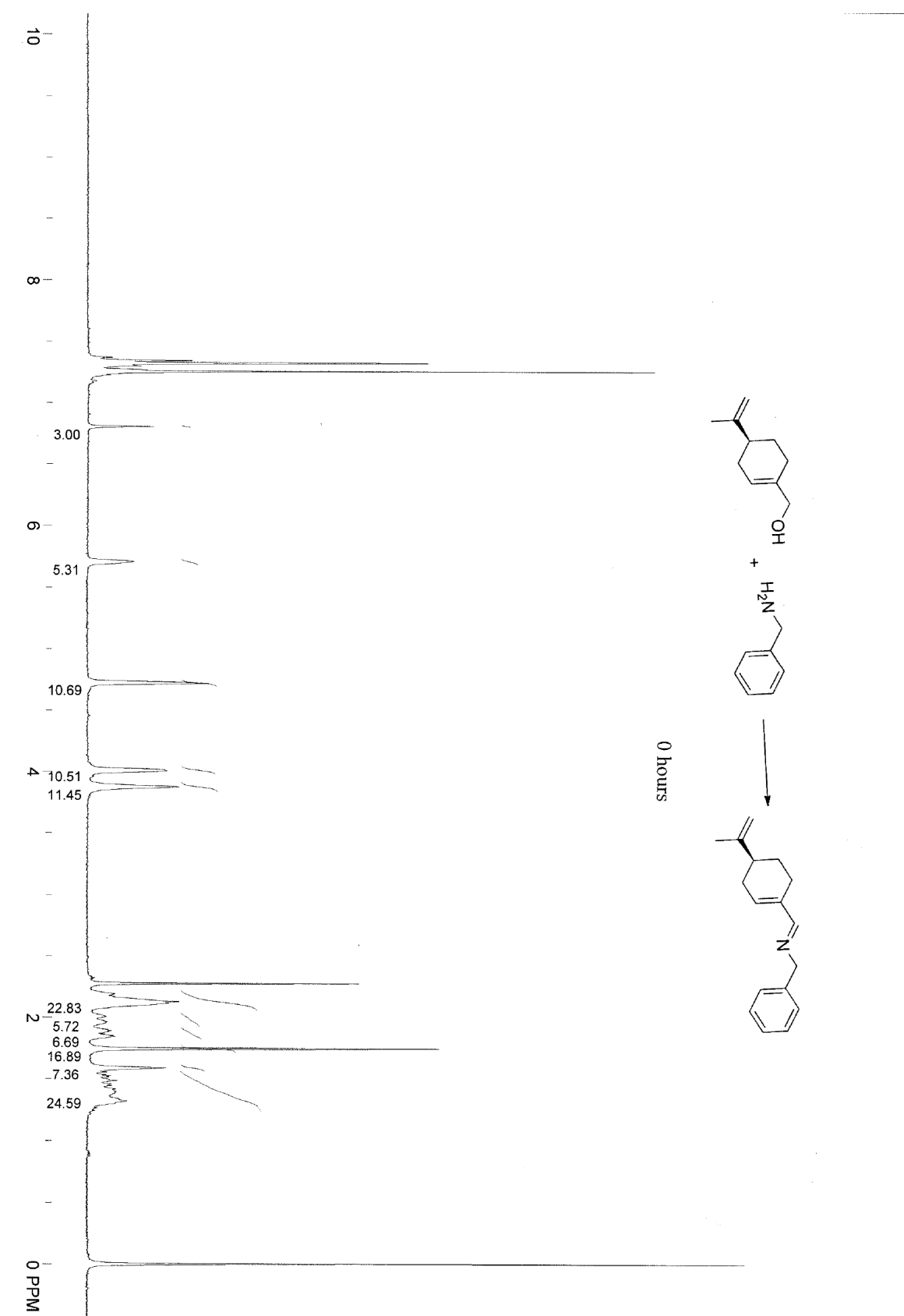
Compound 13.



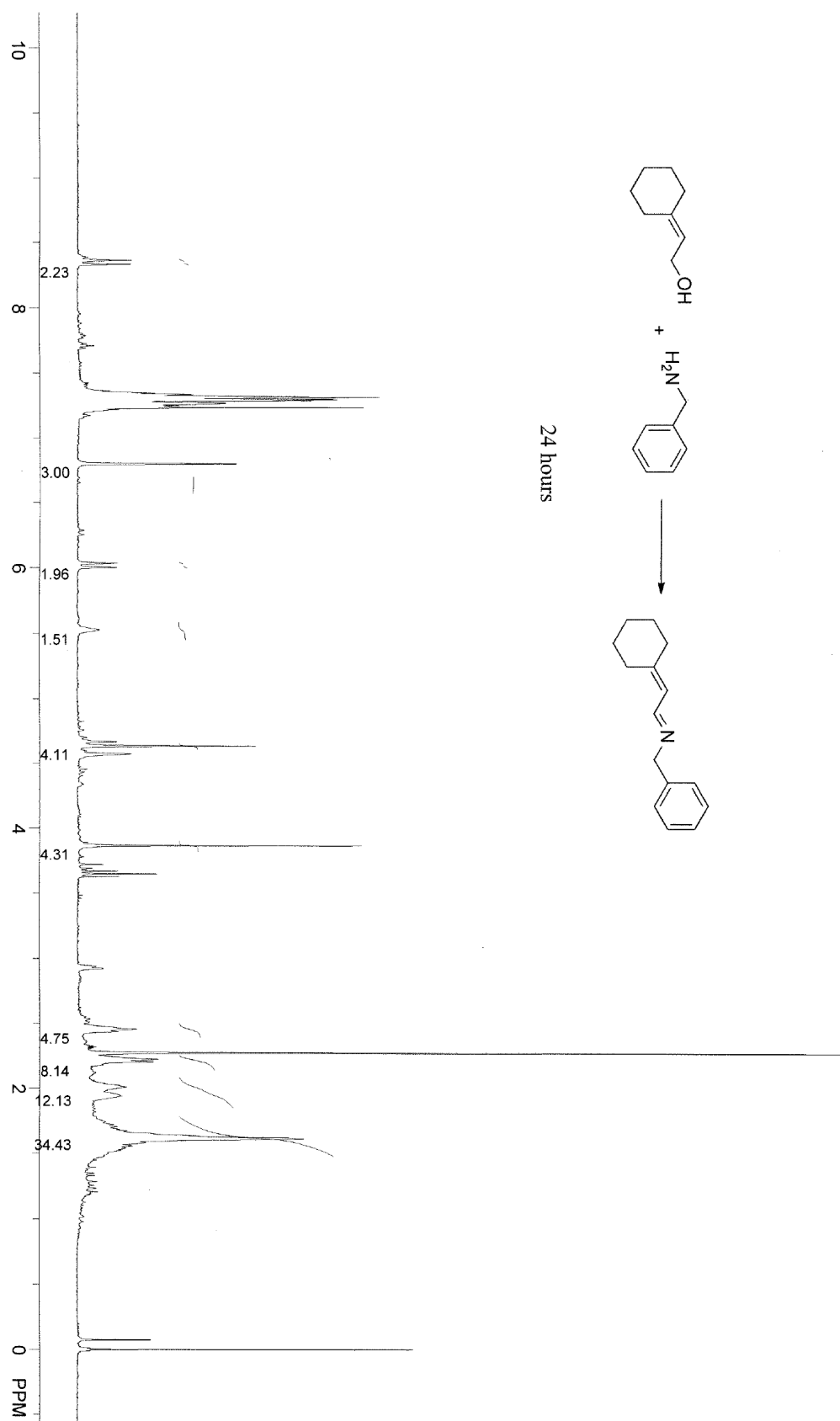
Reaction of 3c to 12 (Table 2, entry 9).



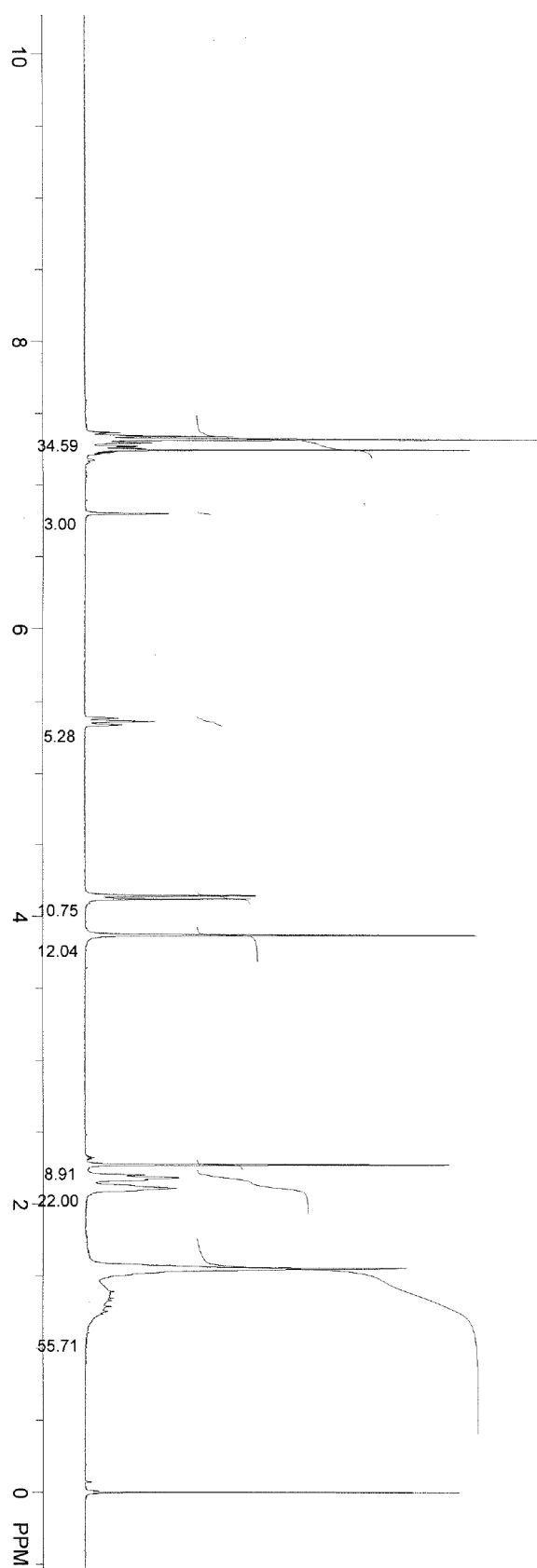
Reaction of 3c to 12 (Table 2, entry 9).



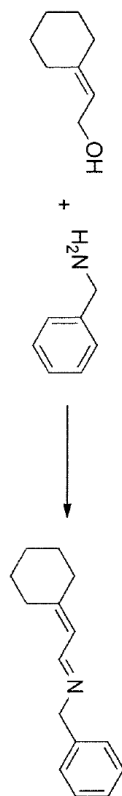
Reaction of 3e to 14 (Table 2, entry 10).



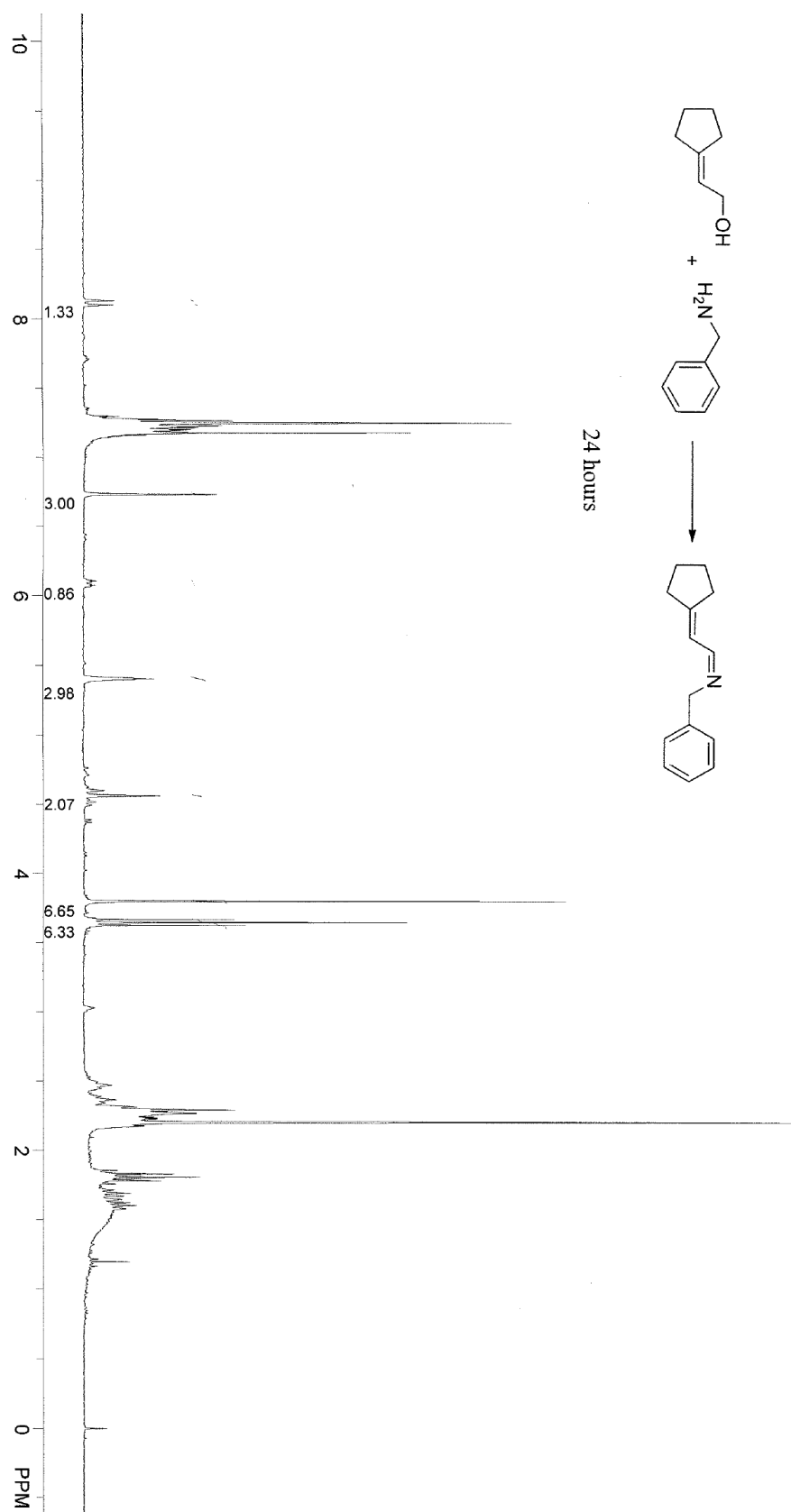
Reaction of 3e to 14 (Table 2, entry 10).



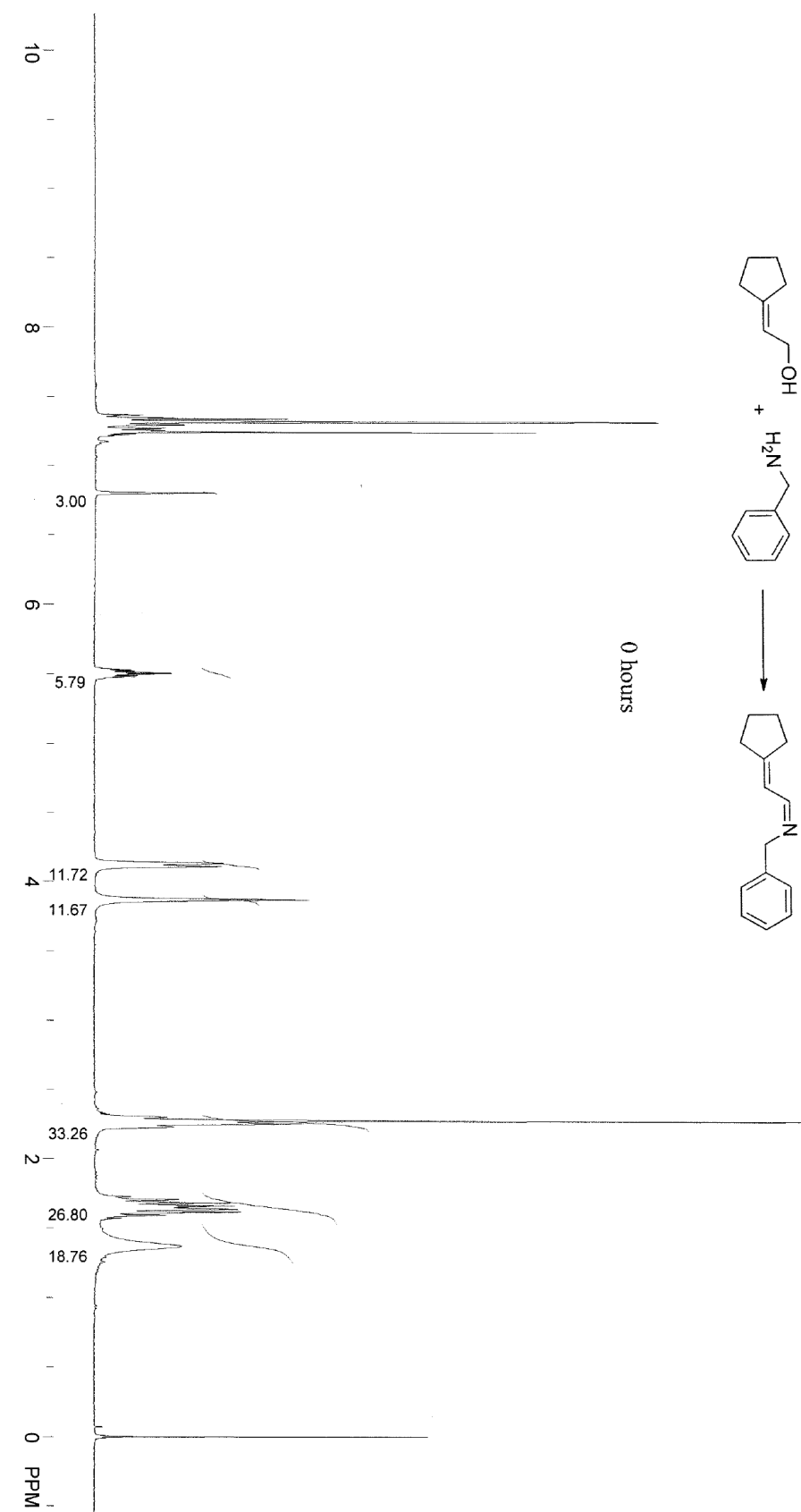
0 hours



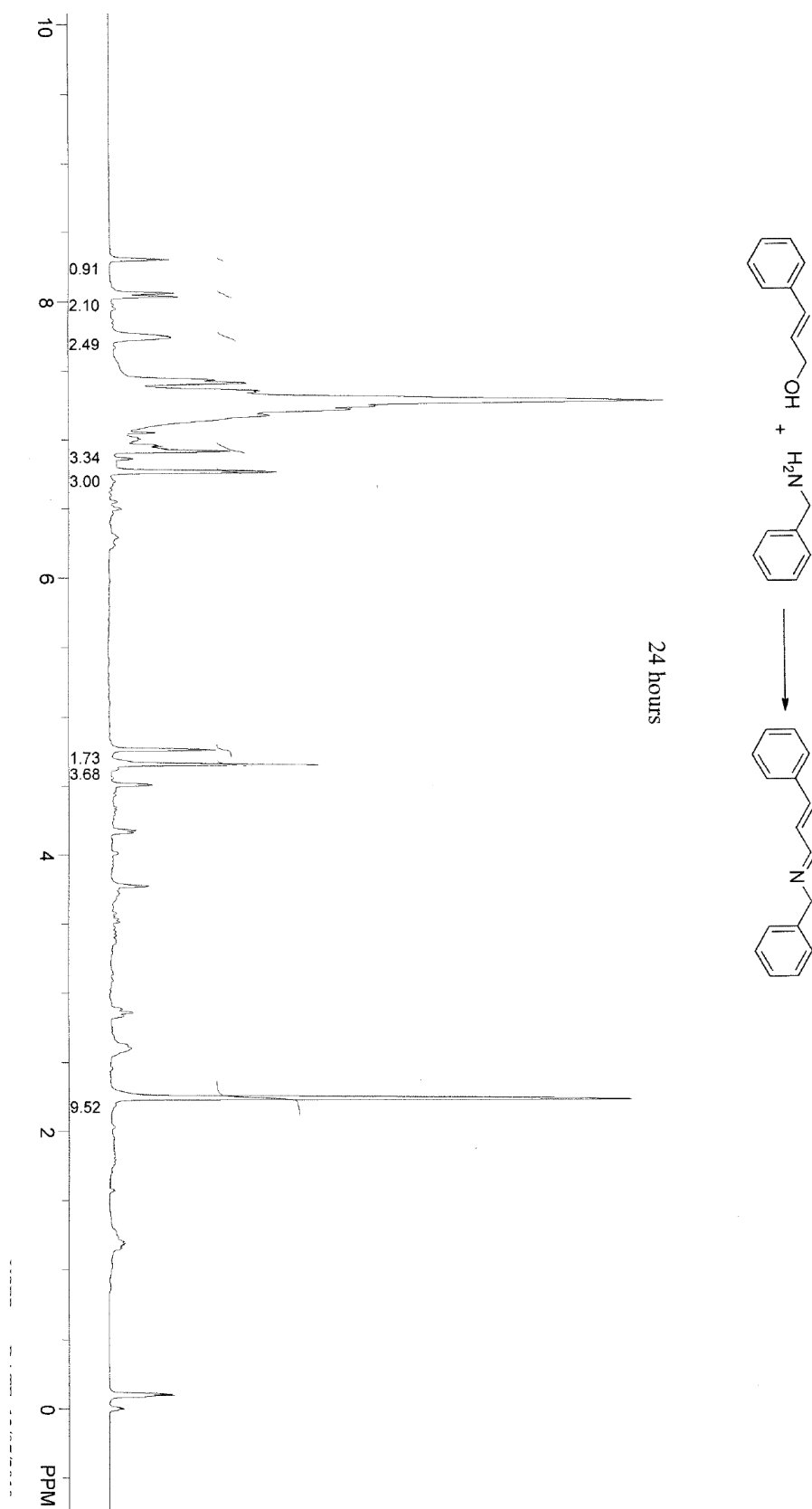
Reaction of 3f to 15 (Table 2, entry 11).



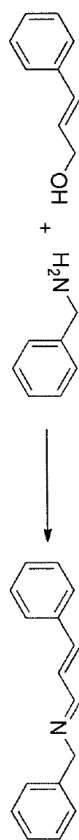
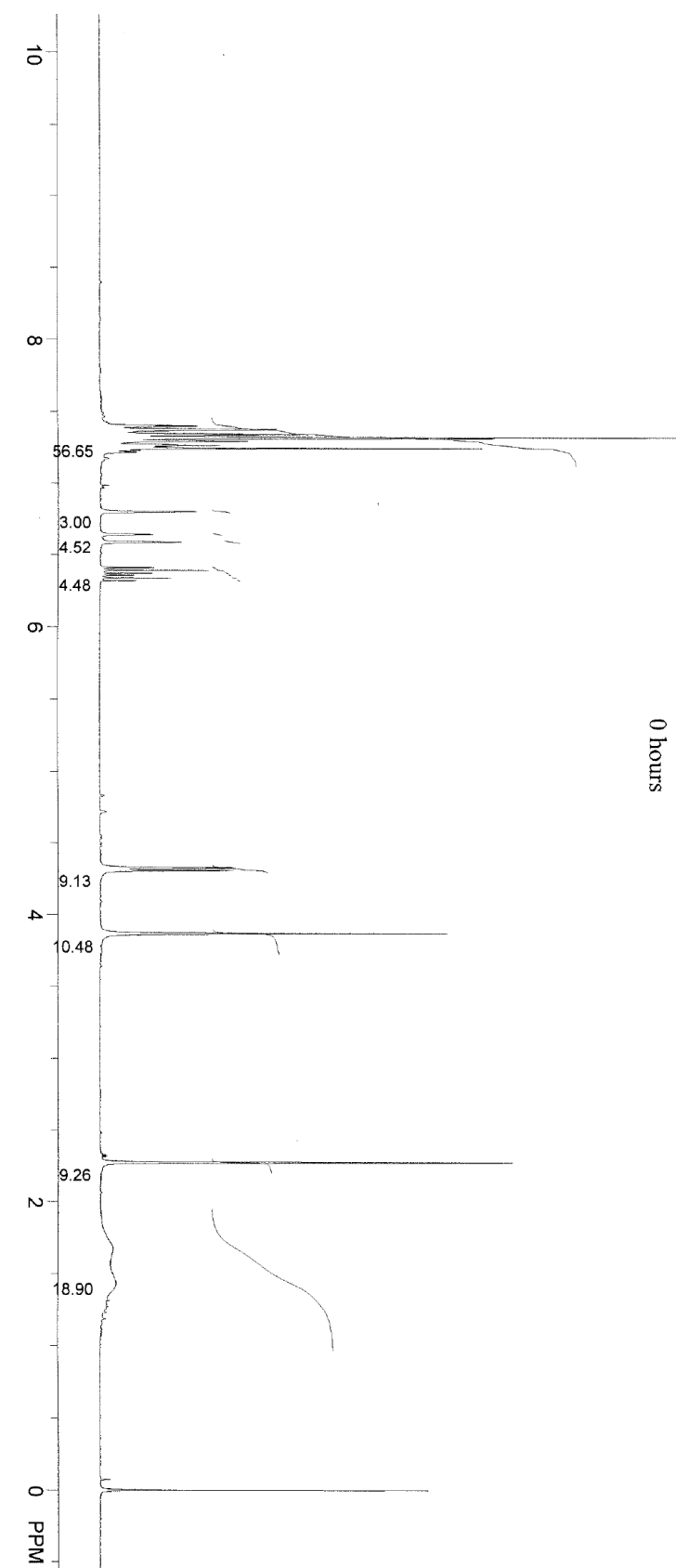
Reaction of 3f to 15 (Table 2, entry 11).



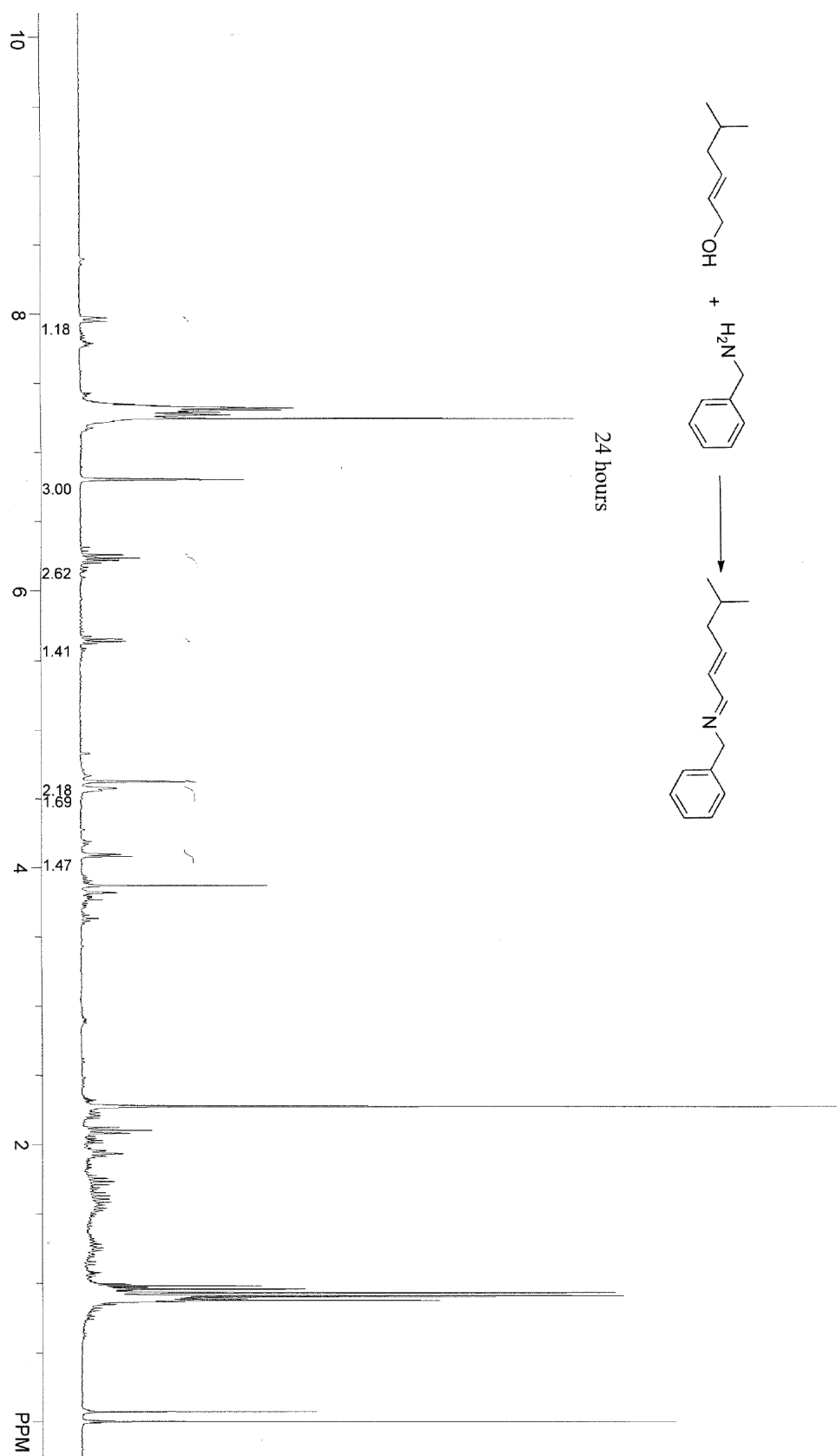
Reaction of 3g to 16 (Table 2, entry 12).



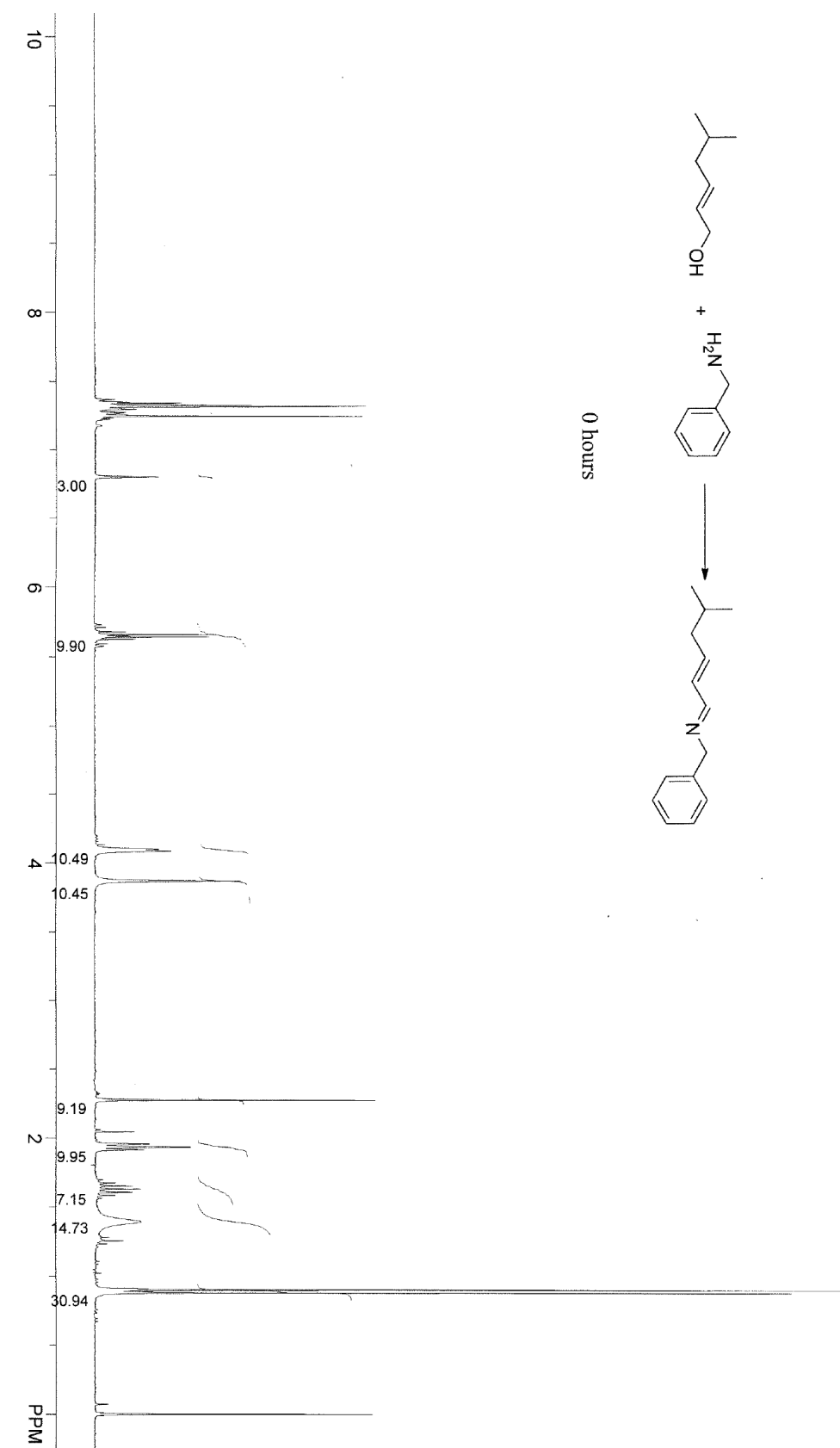
Reaction of 3g to 16 (Table 2, entry 12).



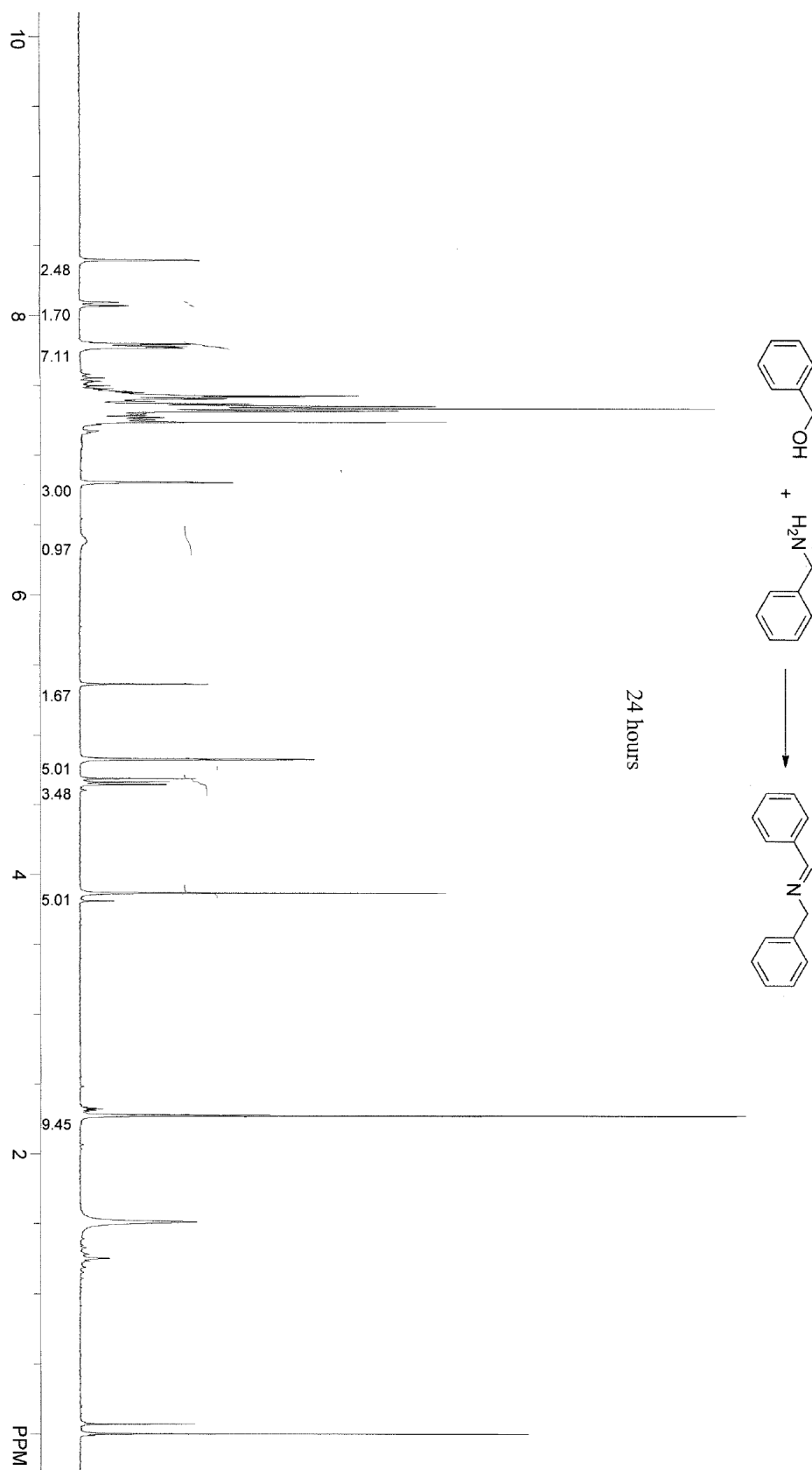
Reaction of 3h to 17 (Table 2, entry 13).



Reaction of 3h to 17 (Table 2, entry 13).



Reaction of 3i to 18 (Table 2, entry 14).



Reaction of 3i to 18 (Table 2, entry 14).

