Generation of quaternary centers by reductive cross-coupling: shifting of regioselectivity in a subset of allylic alcohol-based coupling reactions

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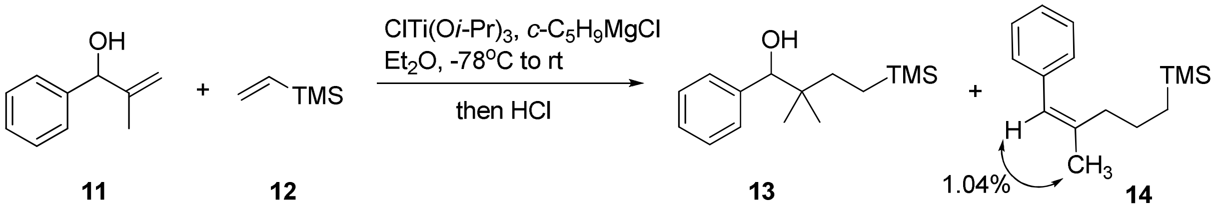
Supporting Information

General information. All reactions were conducted in flame-dried glassware under argon using anhydrous solvents. Tetrahydrofuran, diethyl ether, and dimethylformamide were used after passing through activated alumina columns. Vinyltrimethylsilane and chlorovinyldimethylsilane were distilled prior to use. All other commercially available reagents were used as received.

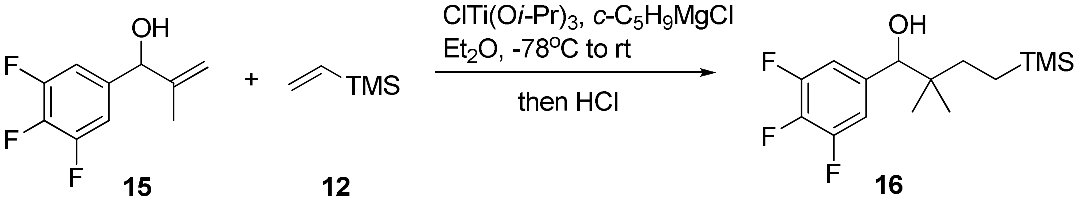
^{1}H NMR data were recorded at 500 MHz or 400 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR data were recorded at 126 MHz or 100 MHz using a Bruker AM-500, Bruker Avance DPX-500 instrument or Bruker AM-400 instrument. ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded using a Thermo Electron Nicolet 6700 FT-IR Spectrometer or a Perkin Elmer Spectrum One FT-IR Spectrometer. Low resolution mass spectrometry was performed on an Agilent Technologies 6890 Network GC System with a 5973 Network Mass Selective Detector or a Varian 500-MS Mass Spectrometer. Chromatographic purifications were performed using 60Å, 35-75μm particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise.



Synthesis of 2,2-dimethyl-1-phenyl-4-(trimethylsilyl)butan-1-ol (13) and (*Z*)-trimethyl(4-methyl-5-phenylpent-4-enyl)silane (14): To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **11** (100 mg, 0.67 mmol) in THF (1.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (317 µL, 2.5 M in hexanes, 0.79 mmol) was added dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min at this temperature before cooling to –78 °C. Ether (20 ml), vinyltrimethylsilane **12** (200 mg, 2.0 mmol), ClTi(O*i*-Pr)$_3$ (2.0 ml, 1.0 M in hexanes, 2.0 mmol), and *c*-C_5H_9MgCl (2.0 ml, 2.0 M in diethyl ether; 4.0 mmol) were then added sequentially to the cooled solution. The resulting yellow solution was slowly warmed to 0 °C over 2 h, during which time it became a thick brown mixture. After stirring at 0 °C for 30 min, 1 N HCl (3 ml) was added and the resulting solution was stirred rapidly for 20 min at rt. This solution was filtered through a pad of silica gel to remove water and titanium salts and the silica gel was subsequently rinsed with 150 ml of EtOAc. The crude material was then purified by flash column chromatography on silica gel (2.5% to 10% ethyl acetate-hexanes) to provide 71 mg (42% yield) of product **13** and 70 mg (45% yield) of product **14** .

Data for 2,2-dimethyl-1-phenyl-4-(trimethylsilyl)butan-1-ol (13): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.20 (m, 5H), 4.47 (d, *J* = 2.0 Hz, 1H), 1.74 (d, *J* = 2.0 Hz, 1H), 1.35 (ddd, *J* = 13.6, 11.0, 6.9 Hz, 1H), 1.19 (ddd, *J* = 13.8, 11.0, 6.9 Hz, 1H), 0.83 (s, 3H), 0.72 (s, 3H), 0.50-0.39 (m, 2H), -0.05 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 127.8, 127.5, 127.2, 80.4, 38.6, 33.0, 22.8, 22.0, 9.9, -1.8; IR (thin film, NaCl) 3452, 3085, 3063, 2955, 2894, 1452, 1419, 1290, 1248, 1180, 1080, 1041, 1001, 863, 836, 783, 703 cm^{-1}; LRMS (EI, M$^{+\cdot}$); calcd for $C_{15}H_{26}OSi$, 250.18 *m/z* (M)$^+$; observed, 250.2 (M)$^+$ *m/z*.

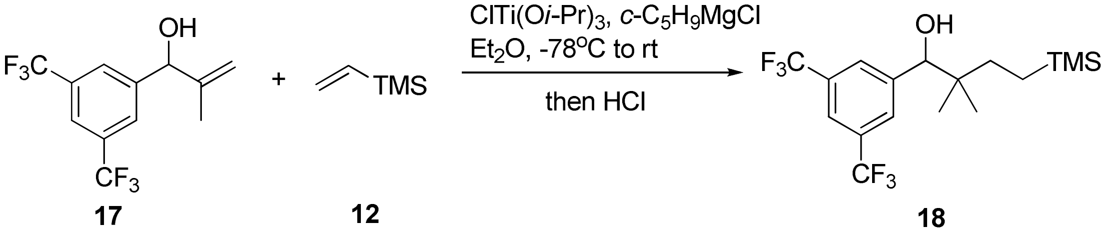
Data for (*Z*)-trimethyl(4-methyl-5-phenylpent-4-enyl)silane (14): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 6.31 (s, 1H, =CH), 2.27 (t, *J* = 8.0 Hz, 2H), 1.92 (s, 2H, CH_3), 1.55 (m, 2H), 0.53 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4 (s), 140.3 (s), 130.3(d), 129.7 (d), 127.5 (d), 127.2 (d), 38.0 (t), 25.7 (q), 24.2 (t), 18.4 (t), 0.0 (q); IR (thin film, NaCl) 3584, 2953, 1650, 1599, 1494, 1441, 1248, 836 cm^{-1}; LRMS $C_{15}H_{24}Si + H^+$, calcd. *m/z* 233.16, observed *m/z* 233.2.



Synthesis of 2,2-dimethyl-1-(3,4,5-trifluorophenyl)-4-(trimethylsilyl)butan-1-ol (16): To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **15** (100 mg, 0.49 mmol) in THF (1.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (232 µL, 2.5 M in hexanes, 0.58 mmol) was added dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min, after which time it was cooled to –78 °C. Ether (14 ml), vinyltrimethylsilane **12** (214 µL, 1.5 mmol), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.5 ml, 1.0 M in hexanes, 1.5 mmol), and *c*-C_5H_9MgCl (1.5 ml, 2.0 M in diethyl ether; 3.0 mmol) were then added sequentially to the cooled solution. The yellow solution was slowly warmed to 0 °C over 2 h, during which time it became a thick brown mixture. After stirring at 0 °C for 30 min, the mixture was quenched with 1

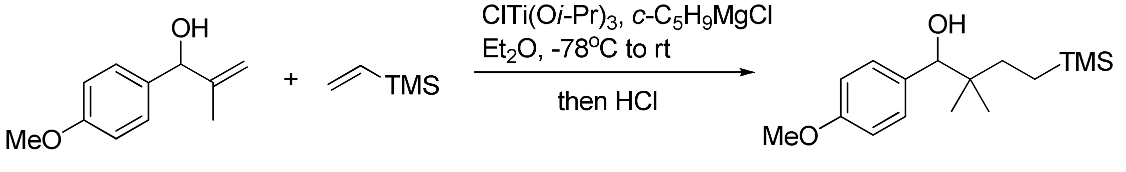
N HCl (3 ml) and stirred rapidly for 20 min at rt. This solution was filtered through a pad of silica gel to remove water and titanium salts and the silica gel was subsequently rinsed with 150 ml of EtOAc. After concentration *in vacuo*, the product was purified by flash column chromatography on silica gel (10 % ethyl acetate-hexanes). Purification afforded product **16** (72 mg, 0.24 mmol) in 49 % yield.

Data for 2,2-dimethyl-1-(3,4,5-trifluorophenyl)-4-(trimethylsilyl)butan-1-ol (16): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97-6.90 (m, 2H), 4.45 (d, *J* = 3.2 Hz, 1H), 1.83 (d, *J* = 3.2 Hz, 1H), 1.41-1.33 (m, 1H), 1.24-1.15 (m, 1H), 0.84 (s, 3H), 0.75 (s, 3H), 0.51-0.40 (m, 2H), -0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5 and 149.5 (m, 1 carbon), 139.7 and 137.7 (m, 1 carbon), 138.5 (m), 111.6 (m), 79.0, 38.7, 32.9, 22.7, 21.8, 9.8, -1.9; IR (thin film, NaCl) 3623, 3456, 2957, 1619, 1530, 1473, 1445, 1344, 1249, 1202, 1121, 1039, 862, 835, 756, 704 cm^{-1}; LRMS (EI, $M^{+\cdot}$); calcd for $C_{15}H_{23}F_3OSi$, 304.15 *m/z* $(M)^+$; observed, 304.1 $(M)^+$ *m/z*.



Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethyl-4-(trimethylsilyl)butan-1-ol (18): To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **17** (100 mg, 0.35 mmol) in THF (1.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (160 μL, 2.5 M in hexanes, 0.40 mmol) was added dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min, after which time it was cooled to –78 °C. Ether (10 ml), vinyltrimethylsilane **12** (152 µL, 1.0 mmol), ClTi(O*i*-Pr)$_3$ (1.0 ml, 1.0 M in hexanes, 1.0 mmol), and *c*-C$_5$H$_9$MgCl (1.0 ml, 2.0 M in diethyl ether; 2.0 mmol) were then added sequentially to the cooled solution. The yellow solution was slowly warmed to 0 °C over 2 h, during which time it became a thick brown mixture. After stirring at 0 °C for 30 min, the mixture was quenched with 1 N HCl (3 ml) and stirred rapidly for 20 min at rt. This solution was filtered through a pad of silica gel to remove water and titanium salts and the silica gel was subsequently rinsed with 150 ml of EtOAc. After concentration *in vacuo*, the product was purified by flash column chromatography on silica gel (10 % ethyl acetate-hexanes). Purification afforded product **18** (65 mg, 0.17 mmol) in 48 % yield.

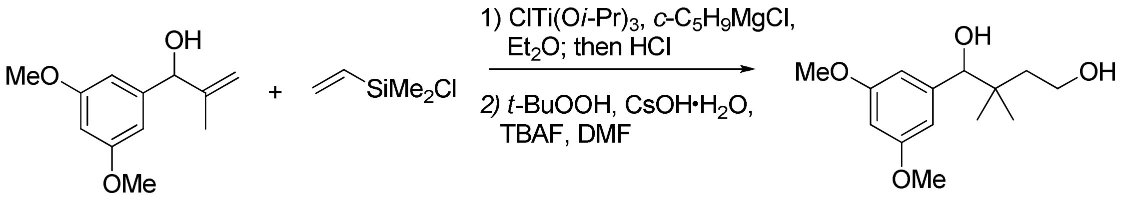
Data for 1-(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethyl-4-(trimethylsilyl)butan-1-ol 18: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80-7.76 (m, 3H), 4.65 (d, *J* = 3.1 Hz, 1H), 1.57 (d, *J* = 0.6 Hz, 1H), 1.44-1.34 (m, 1H), 1.24-1.16 (m, 1H), 0.86 (s, 3H), 0.77 (s, 3H), 0.52-0.42 (m, 2H), -0.02 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.7, 130.8 (q, *J* = 33 Hz), 127.9, 123.3 (q, *J* = 272 Hz), 121.2 (m), 79.3, 38.8, 32.8, 22.4, 21.8, 9.8, -2.0; IR (thin film, NaCl) 3441, 2960, 1625, 1467, 1379, 1278, 1139, 1047, 1003, 901, 844, 776, 740, 710, 682, 610 cm^{-1}; LRMS (EI, M$^{+\cdot}$); calcd for C$_{17}$H$_{24}$F$_6$OSi, 386.15 *m/z* (M)$^+$; observed, 386.10 (M)$^+$ *m/z*.



19 **12** **20**

Synthesis of 1-(4-methoxyphenyl)-2,2-dimethyl-4-(trimethylsilyl)butan-1-ol (20): To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **19** (100 mg, 0.56 mmol) in THF (1.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (264 μL, 2.5 M in hexanes, 0.66 mmol) was added dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min, after which time it was cooled to –78 °C. Ether (16 ml), vinyltrimethylsilane **12** (255 μL, 1.6 mmol), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.6 ml, 1.0 M in hexanes, 1.6 mmol), and $\textit{c}\text{-}C_5H_9MgCl$ (1.6 ml, 2.0 M in diethyl ether; 3.2 mmol) were then added sequentially to the cooled solution. The yellow solution was slowly warmed to 0 °C over 2 h, during which time it became a thick brown mixture. After stirring at 0 °C for an additional hour, 1 N HCl (5 ml) was added, and the mixture was stirred rapidly for 20 min at rt. This solution was then partitioned between EtOAc (20 ml) and water (20 ml). The aqueous layer was extracted with EtOAc (3 x 10 ml) and the combined organic layer was washed with $NaHCO_3$ (aq., sat) and brine, before being dried over Na_2SO_4. After filtration and concentration *in vacuo*, the product was purified by flash column chromatography on silica gel (10 % ethyl acetate-hexanes). Purification afforded product **20** (73 mg, 0.26 mmol) in 48 % yield.

Data for 1-(4-methoxyphenyl)-2,2-dimethyl-4-(trimethylsilyl)butan-1-ol (20): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.47 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H), 1.69 (d, *J* = 2.8 Hz, 1H), 1.40-1.32 (m, 1H), 1.26-1.18 (m, 1H), 0.86 (s, 3H), 0.74 (s, 3H), 0.53-0.42 (m, 2H), -0.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 134.5, 128.7, 112.9, 80.1, 55.2, 38.7, 32.9, 22.7, 22.0, 9.9, -1.8; IR (thin film, NaCl) 3476, 2955, 1612, 1513, 1249, 1175, 1038, 835, 756 cm^{-1}; LRMS (EI, $M^{+\cdot}$); calcd for $C_{16}H_{28}O_2Si$, 280.19 *m/z* $(M)^+$; observed, 280.1 $(M)^+$ *m/z*.



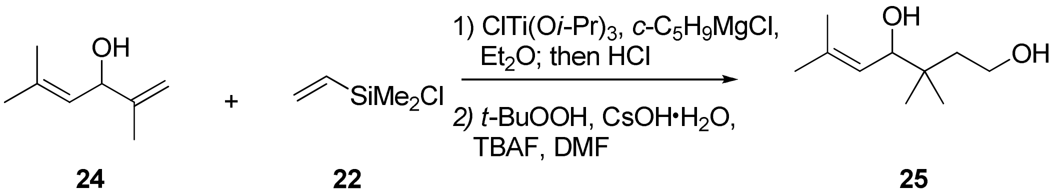
21 **22** **23**

Synthesis of 1-(3,5-dimethoxyphenyl)-2,2-dimethylbutane-1,4-diol (23): To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added ether (7 ml) and chlorodimethylvinylsilane **22** (97 µL, 0.7 mmol), then cooled to –78 °C. ClTi(O*i*-Pr)$_3$ (700 µL, 1.0 M in hexanes, 0.7 mmol) and *c*-C$_5$H$_9$MgCl (700 µL, 2.0 M in diethyl ether, 1.4 mmol) were then added sequentially, and the solution was allowed to rapidly warm to –50 °C. The solution was stirred at –50 °C for 2 h before cooling back to –78 °C (during this time the solution turned from a bright yellow color to dark brown).

To a separate flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **21** (50 mg, 0.24 mmol) in THF (1.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (113 µL, 2.5 M in hexanes, 0.28 mmol) was added slowly dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min before being transferred via cannula to the dark brown mixture. The solution was then slowly warmed to 0 °C over 2 h. After stirring at 0 °C for 30 min, 1 N HCl (3 ml) was added, and the mixture was rapidly stirred for 20 min at rt. This solution was filtered through a pad of silica gel to remove water and titanium salts and the silica gel was subsequently rinsed with 150 ml of EtOAc. After concentration *in vacuo*, the crude product was used in the following reaction without purification.

To a cooled (0 °C) solution of *t*-BuOOH (1.8 ml, ~5.5 M in decane, 9.8 mmol) in DMF (7 ml) was added CsOH•H$_2$O (1.4 g, 8.5 mmol). After the mixture was warmed to rt, a solution of the crude isopropoxysilane in DMF (1.0 ml) was added dropwise by syringe. After 10 min, TBAF (3.5 ml, 1.0 M in THF, 3.5 mmol) was added, and the mixture was warmed to 70 °C and stirred at that temperature for 4 h. The mixture was cooled to rt, and $Na_2S_2O_3$ was added. The mixture was then partitioned between water (45 ml) and ether (45 ml). The aqueous layer was extracted with ether (3 x 20 ml) and the combined organic layer was washed with $NaHCO_3$ (aq., sat) and brine, before being dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude material was purified by flash column chromatography on silica gel (50% ethyl acetate-hexanes) to provide product **22** (28 mg, 0.12 mmol) in 49% yield (2 steps).

Data for 1-(3,5-dimethoxyphenyl)-2,2-dimethylbutane-1,4-diol (22): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (d, J = 2.2 Hz, 2H), 6.37 (app t, J = 2.4 Hz, 1H), 4.42 (s, 1H), 3.82-3.75 (m, 2H), 3.78 (s, 6H), 3.15 (br s, 1H), 2.66 (br s, 1H), 1.81 (ddd, J = 14.5, 7.2, 5.4 Hz, 1H), 1.51 (ddd, J = 14.5, 6.3, 5.0 Hz, 1H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 144.2, 106.2, 99.1, 81.1, 59.4, 55.3, 42.5, 37.9, 25.7, 23.2; IR (thin film, NaCl) 3320, 2960, 1597, 1458, 1429, 1345, 1293, 1204, 1155, 1063, 843, 698 cm^{-1}; LRMS (EI, $M^{+\cdot}$); calcd for $C_{14}H_{22}O_4$, 254.15 *m/z* $(M)^+$; observed, 254.2 $(M)^+$ *m/z*.



24 **22** **25**

Synthesis of 3,3,6-trimethylhept-5-ene-1,4-diol 25: To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added ether (12 ml) and chlorodimethylvinylsilane **22** (161 µL, 1.1 mmol). The solution was cooled to –78 °C and ClTi(O*i*-Pr)$_3$ (1.1 ml, 1.0 M in hexanes, 1.1 mmol) and *c*-C_5H_9MgCl (1.1 ml, 2.0 M in diethyl ether, 2.2 mmol) were added sequentially. This mixture was rapidly warmed to –50 °C and maintained at this temperature for 2 h before cooling to –78 °C (during this time the solution turned from a bright yellow color to dark brown).

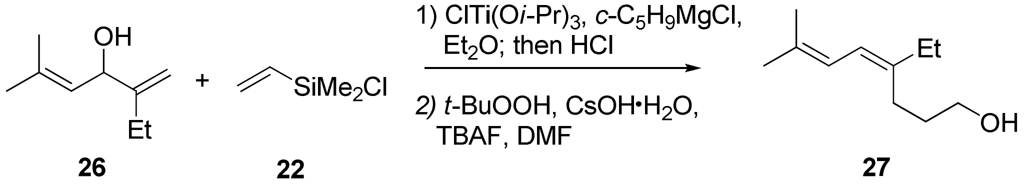
To a separate flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **24** (54 mg, 0.40 mmol) in THF (1.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (185 µL, 2.5 M in hexanes, 0.46 mmol) was added dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min before being transferred via cannula to the dark brown mixture.

The combined mixture was slowly warmed to 0 °C over 2 h. After stirring at 0 °C for an additional hour, 1 N HCl (5 ml) was added, and the mixture was stirred rapidly for 20 min at rt. This solution was partitioned between EtOAc (20 ml) and water (20 ml). The aqueous layer was extracted with EtOAc and the combined organic layer was then washed with $NaHCO_3$ (aq., sat) and brine, before being dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude product was used in the following reaction.

To a cooled (0 °C) solution of *t*-BuOOH (2.9 ml, ~5.5 M in decane, 16 mmol) in DMF (10 ml) was added $CsOH{\bullet}H_2O$ (2.3 g, 14 mmol). After the mixture was warmed to rt, a solution of crude isopropoxysilane in DMF (1.0 ml) was added dropwise by syringe. After 10 min, TBAF (5.8 ml, 1.0 M in THF, 5.8 mmol) was added and the mixture was heated to 70 °C. After stirring at 70 °C for 4 h, the solution was cooled to rt and $Na_2S_2O_3$ was added. The mixture was then partitioned between water (25 ml) and EtOAc (25 ml). The aqueous layer was extracted with EtOAc (3 x 20 ml) and the combined organic layer was then washed with $NaHCO_3$ (aq., sat) and brine, before being dried over Na_2SO_4.

After filtration and concentration *in vacuo*, the crude material was then purified by flash column chromatography on silica gel (50% ethyl acetate-hexanes) to provide product **25** (40 mg, 0.23 mmol) in 59 % yield (2 steps).

Data for 3,3,6-trimethylhept-5-ene-1,4-diol, 25: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34-5.29 (m, 1H), 4.10 (d, *J* = 9.5 Hz, 1H), 3.76-3.66 (m, 2H), 3.00-2.70 (br s, 2H), 1.78-1.72 (m, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.48-1.41 (m, 1H), 0.91 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 124.3, 74.9, 59.1, 42.3, 37.7, 26.1, 24.7, 23.7, 18.5; IR (thin film, NaCl) 3310, 2961, 2930, 1673, 1448, 1384, 1363, 1283, 1034, 1010, 981, 897 cm^{-1}; LRMS (EI, Na) calcd for $C_{10}H_{20}O_2Na$, 195.15 *m/z* (M + Na)$^+$; observed, 195.08 (M + Na)$^+$ *m/z*.



Synthesis of (*Z*)-4-ethyl-7-methylocta-4,6-dien-1-ol (27): To a flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added ether (12 ml) and chlorodimethylvinylsilane **22** (240 mg, 2.0 mmol). The solution was cooled to –78 °C and $ClTi(Oi\text{-}Pr)_3$ (2.0 ml, 1.0 M in hexanes, 2.0 mmol) and $c\text{-}C_5H_9MgCl$ (2.0 ml, 2.0 M in diethyl ether, 4.0 mmol) were added sequentially. This mixture was rapidly warmed to –50 °C and maintained at this temperature for 2 h before cooling to –78 °C (during this time the solution turned from a bright yellow color to dark brown).

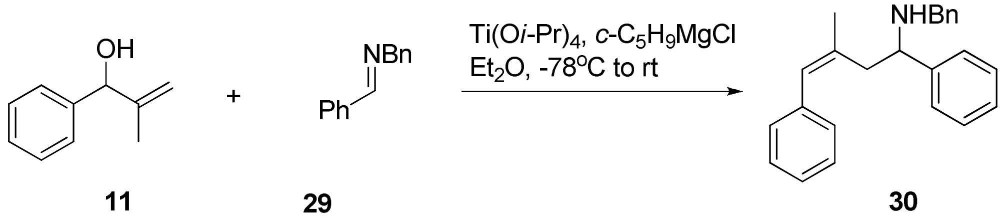
To a separate flame-dried flask equipped with a magnetic stir-bar and flushed with argon was added the allylic alcohol **26** (140 mg, 1.0 mmol) in THF (2.0 ml). The solution was cooled to –78 °C, and *n*-BuLi (440 µL, 2.5 M in hexanes, 1.1 mmol) was added dropwise over 2 min. The solution was rapidly warmed to 0 °C and stirred for 15 min before being transferred via cannula to the dark brown mixture.

The combined mixture was slowly warmed to 0 °C over 2 h. After stirring at 0 °C for an additional hour, 1 N HCl (5 ml) was added, and the mixture was stirred rapidly for 20 min at rt. This solution was partitioned between EtOAc (20 ml) and water (20 ml). The aqueous layer was extracted with EtOAc and the combined organic layer was then washed with $NaHCO_3$ (aq., sat) and brine, before being dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude product was used in the following reaction.

To a cooled (0 °C) solution of *t*-BuOOH (2.9 ml, ~5.5 M in decane, 16 mmol) in DMF (10 ml) was added $CsOH \bullet H_2O$ (2.3 g, 14 mmol). After the mixture was warmed to rt, a solution of crude isopropoxysilane in DMF (1.0 ml) was added dropwise by syringe. After 10 min, TBAF (5.8 ml, 1.0 M in THF, 5.8 mmol) was added and the mixture was heated to 70 °C. After stirring at 70 °C for 4 h, the solution was cooled to rt and $Na_2S_2O_3$ was added. The mixture was then partitioned between water (25 ml) and EtOAc (25 ml). The aqueous layer was extracted with EtOAc (3 x 20 ml) and the combined organic layer was then washed with $NaHCO_3$ (aq., sat) and brine, before being dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude material was then purified by flash column chromatography on silica gel (20% ethyl acetate-hexanes) to provide product **27** (123 mg, 0.73 mmol) in 73 % yield (2 steps).

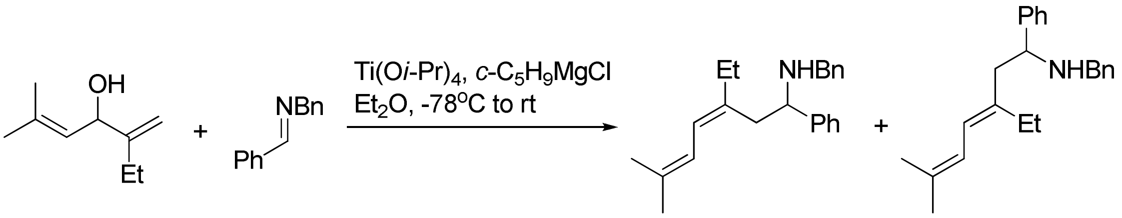
Data for (*Z*)-4-ethyl-7-methylocta-4,6-dien-1-ol (27): ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (ABq, 2H, =CH-CH=), 3.71 (t, *J* = 6.4 Hz, 2H, $C\underline{H_2}OH$), 2.31 (t, *J* = 7.6 Hz, 2H,

CH_2), 2.18 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 1.86 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.73 (m, 2H, CH_2), 1.67 (br s, 1H, OH), 1.11 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1 (s), 133.4 (s), 120.7 (d), 120.3 (d), 62.9 (t), 31.4 (t), 30.1 (t), 26.6 (t), 26.4 (q), 18.1 (q), 12.9 (q); IR (thin film, NaCl) 3400, 2971, 1668, 1455, 1377, 1060, 761 cm^{-1}; LRMS $C_{11}H_{20}O + H^+$ calcd. *m/z* 169.15, observed *m/z* 169.3.



Synthesis of (*Z*)-*N*-benzyl-3-methyl-1,4-diphenylbut-3-en-1-amine (30): To a solution of 390 mg (2.0 mmol) of imine **29** in 8 mL of dry diethyl ether was added 0.89 mL (850 mg, 3.0 mmol) of Ti(O*i*-Pr)$_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 3.0 mL (2.0 M, 6.0 mmol) of *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of the lithium alkoxide of alcohol **11** in 2 mL of THF, prepared by deprotonation of 148 mg (1.0 mmol) of alcohol **29** at -78 °C with 0.44 mL (2.5 M, 1.1 mmol) of *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1) to give 284 mg (87%) of amine **30** as a colorless oil.

Data for (*Z*)-*N*-benzyl-3-methyl-1,4-diphenylbut-3-en-1-amine (30): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m 15H), 6.42 (s, 1H, =CH), 3.89 (dd, *J* = 9.2, 6.0 Hz, 1H, C<u>H</u>NHBn), 3.70 and 3.48 (ABq, *J* = 13.6 Hz, 2H, NC$\underline{H}_2$Ph), 2.88 (dd, *J* = 13.6, 8.8 Hz, 1H, C$\underline{H}_2$), 2.34 (dd, *J* = 13.6, 6.0 Hz, 1H, C$\underline{H}_2$), 1.79 (s, 3H, CH_3), 1.59 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) 144.1 (s), 140.7 (s), 138.0 (s), 135.7 (s), 128.91 (d), 128.86 (d), 128.36 (d), 128.29 (d), 128.06 (d), 128.01 (d), 127.33 (d), 127.04 (d), 126.76 (d), 126.12 (d), 59.94 (d), 51.41 (t), 41.61 (t), 23.95 (q); IR (thin film, NaCl) 3322, 3081, 2850, 1599, 1492, 1453, 1114, 1027, 844, 699 cm^{-1}; LRMS $C_{24}H_{25}N + H^+$ calcd. *m/z* 328.2, observed *m/z* 328.4.

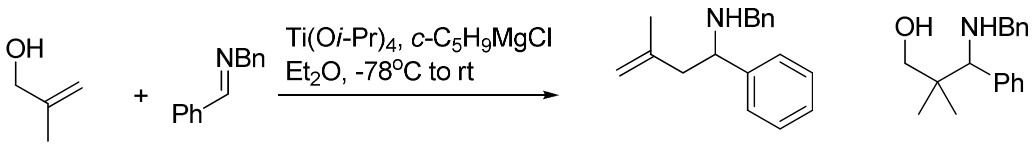


26 **29** **31 (1:0.7 mixture)**

Synthesis of (*Z*)-*N*-benzyl-3-ethyl-6-methyl-1-phenylhepta-3,5-dien-1-amine and (*E*)-*N*-benzyl-3-ethyl-6-methyl-1-phenylhepta-3,5-dien-1-amine (31): To a solution of 390 mg (2.0 mmol) of imine **29** in 8 mL of dry diethyl ether was added 0.89 mL (850 mg, 3.0 mmol) of Ti(O*i*-Pr)$_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 3.0 mL (2.0 M, 6.0 mmol) of *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of the lithium alkoxide of alcohol **26** in 2 mL of THF, prepared by deprotonation of 140 mg (1.0 mmol) of alcohol **29** at -78 °C with 0.44 mL (2.5 M, 1.1 mmol) of *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1) to give 230 mg (72%) of amines **31** as a colorless oil. NMR spectra shown it to be a 1:0.7 mixture of alkene isomers.

Data for (*Z*)-*N*-benzyl-3-ethyl-6-methyl-1-phenylhepta-3,5-dien-1-amine (major product in 31): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 10H), 6.10 (ABq, *J* = 11.2 Hz, 2H, =CH-CH=), 3.78 (dd, *J* = 8.8, 4.8 Hz, 1H, C$\underline{H}$NHBn), 3.71 and 3.50 (ABq, *J* = 14.0 Hz, 2H, NC$\underline{H}_2$Ph), 2.75 (dd, *J* = 13.6, 8.8 Hz, 1H, C$\underline{H}_2$), 2.27 (m, 1H, C$\underline{H}_2$), 1.98 (q, *J* = 7.6 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.86 (s, 3H, CH$_3$), 1.77 (s, 3H, CH$_3$), 1.70 (br s, 1H, NH), 0.99 (t, *J* =7.6 Hz, 2H, CH$_2$C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 147.0 (s), 146.1 (s), 138.3 (s), 133.9 (s), 128.38 (d), 128.32 (d), 128.29 (d), 128.23 (d), 127.30 (d), 126.96 (d), 122.85 (d), 120.89 (d), 60.55 (d), 51.32 (t), 39.96 (t), 30.15 (t), 26.41 (q), 12.89 (q); IR (thin film, NaCl) 3325, 3085, 2874, 1603, 1494, 1454, 1028, 699 cm^{-1}; LRMS (M + H$^+$); calcd for $C_{23}H_{29}N$, 320.2; observed, 320.4.

Data for (*E*)-*N*-benzyl-3-ethyl-6-methyl-1-phenylhepta-3,5-dien-1-amine (minor product of 31): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 10H), 6.03 (ABq, *J* = 11.2 Hz, 2H, =CH-CH=), 3.76 (m, 1H, C$\underline{H}$NHBn), 3.71 and 3.50 (ABq, *J* = 14.0 Hz, 2H, NC$\underline{H}_2$Ph), 2.46 (dd, J = 13.6, 4.0 Hz, 1H, C$\underline{H}_2$), 2.48 (m, 1H, C$\underline{H}_2$), 2.45 (q, J = 7.6 Hz, 2H, C$\underline{H}_2$$CH_3$), 1.82 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.70 (br s, 1H, NH), 0.98 (t, J =7.6 Hz, 2H, CH_2C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 10 peaks of aryl and vinyl carbons overlap with those of the (*Z*)-isomer and can not be differentiated, other peaks are: 123.67 (d), 120.57 (d), 59.86 (d), 51.51 (t), 47.16 (t), 23.09 (t), 18.15 (q), 13.32 (q); IR (thin film, NaCl) 3325, 3085, 2874, 1603, 1494, 1454, 1028, 699 cm^{-1}; LRMS $C_{23}H_{29}N$ + H^+ calcd. *m/z* 320.2, observed *m/z* 320.4.

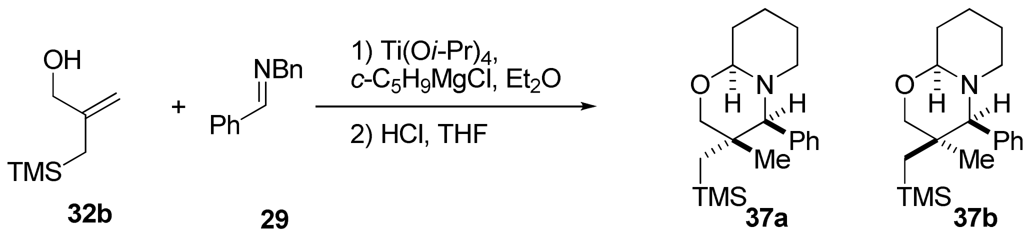


32a **29** **33a** **34a**

Synthesis of (*N*)-benzyl-3-methyl-1-phenylbut-3-en-1-amine (33a) and 3-(benzylamino)-2,2-dimethyl-3-phenylpropan-1-ol (34a): To a solution of 390 mg (2.0 mmol) of imine **29** in 8 mL of dry diethyl ether was added 0.89 mL (850 mg, 3.0 mmol) of Ti(O*i*-Pr)$_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 3.0 mL (2.0 M, 6.0 mmol) of *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of the lithium alkoxide of alcohol **32a** in 2 mL of THF, prepared by deprotonation of 140 mg (1.0 mmol) of alcohol **32a** at -78 °C with 0.44 mL (2.5 M, 1.1 mmol) of *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (10% to 50% ethyl acetate in hexanes) to give 150 mg (60%) of amine **33a** and 60 mg (30%) of aminoalcohol **34a** as colorless oils.

Data for (*N*)-benzyl-3-methyl-1-phenylbut-3-en-1-amine (33a): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 10H), 4.84 (s, 1H, $=CH_2$), 4.79 (s, 1H, $=CH_2$), 3.80 (dd, *J* = 9.2, 4.4 Hz, 1H, C$\underline{H}$NHBn), 3.73 and 3.51 (ABq, *J* = 13.2 Hz, 2H, NC$\underline{H}_2$Ph), 2.41 (dd, *J* = 14.0, 9.2 Hz, 1H, C$\underline{H}_2$), 2.33 (dd, *J* = 14.0, 4.8 Hz, 1H, C$\underline{H}_2$), 1.77 (br s, 1H, NH), 1.68 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 144.33 (s), 142.75 (s), 140.65 (s), 128.40 (d), 128.33 (d), 128.14 (d), 127.30 (d), 127.01 (d), 126.81 (d), 113.41 (t), 59.29 (d), 51.49 (t), 47.64 (t), 22.04 (q); IR (thin film, NaCl) 3326, 3026, 2967, 2800, 1645, 1585, 1493, 1453, 1027, 894, 756, 699 cm^{-1}; LRMS $C_{18}H_{21}N + H^+$, calcd. *m/z* 252.17, observed *m/z* 252.3.

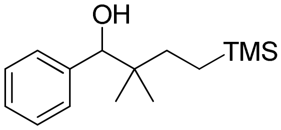
Data for 3-(benzylamino)-2,2-dimethyl-3-phenylpropan-1-ol (34a): ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 10H), 3.64 (s, 1H, C$\underline{H}$NHBn), 3.64 and 3.44 (ABq, 2H, NHC$\underline{H}_2$Ph), 3.60 and 3.48 (ABq, 2H, C$\underline{H}_2$OH), 0.95 (s, 3H, C$\underline{H}_3$), 0.72 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.41 (s), 139.18 (s), 128.56 (d), 128.45 (d), 128.27 (s), 127.39 (s), 127.31 (s), 127.22 (s), 74.50 (t), 71.61 (d), 51.69 (t), 38.30 (s), 24.45 (q), 18.84 (q); IR (thin film, NaCl) 3307, 3062, 2958, 2872, 2100, 1494, 1454, 1028, 749, 699 cm^{-1}; LRMS $C_{18}H_{23}NO + H^+$, calcd. *m/z* 270.18, observed *m/z* 270.3.



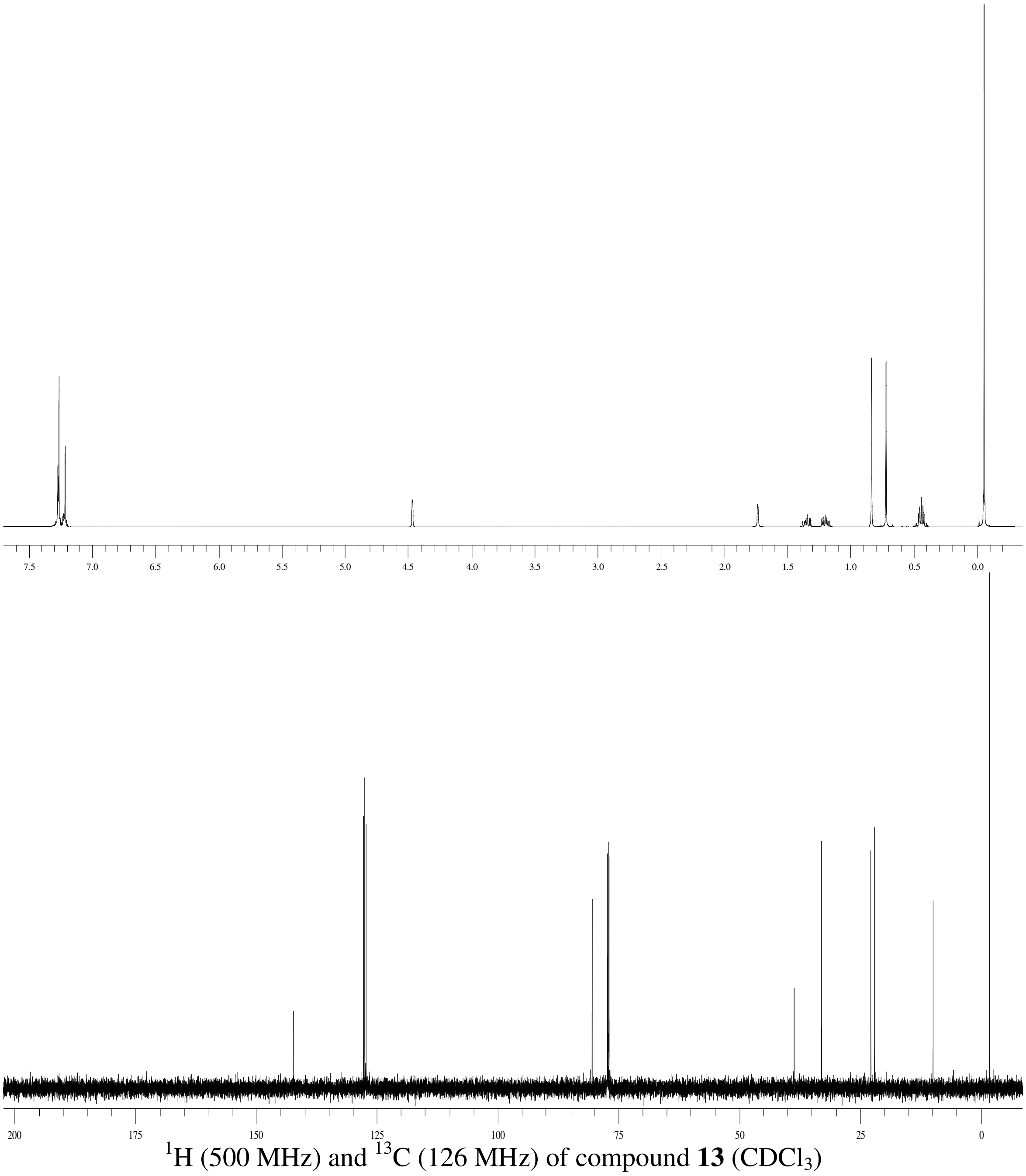
Synthesis of (3*S*,4*S*,9a*S*)-3-methyl-4-phenyl-3-((trimethylsilyl)methyl)-octahydropyrido[2,1-b][1,3]oxazine (37a) and (3*R*,4*S*,9a*S*)-3-methyl-4-phenyl-3-((trimethylsilyl)methyl)octahydropyrido-[2,1-b][1,3]oxazine (37b): To a solution of 312 mg (1.33 mmol) of imine **29** in 8 mL of dry diethyl ether was added 0.59 mL (568 mg, 2.0 mmol) of Ti(O*i*-Pr)$_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 2.0 mL (2.0 M, 4.0 mmol) of c-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of the lithium alkoxide of alcohol **32b** in 2 mL of THF, prepared by deprotonation of 284 mg (2.0 mmol) of alcohol **32b** at -78 °C with 0.88 mL (2.5 M, 2.2 mmol) of *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (20% ethyl acetate in hexanes) to give 292 mg (58%) of coupling product **36** as a colorless oil. To a solution of 100mg of **36** in 1 mL of THF was added 1.25 mL (1.25 mmol) of 1N HCl aqueous solution at rt under argon. After stirring for 1 h, the reaction was quenched by addition of 0.1 g (0.75 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 10 mL of CH_2Cl_2. The organic extract was dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 40:1) to give 60 mg (76%) of oxzaine **37a** and 15 mg (19%) of oxzaine **37b** as colorless oils. Stereochemistry was assigned by nOe.

Data for 3*S*,4*S*,9a*S*)-3-methyl-4-phenyl-3-((trimethylsilyl)methyl)octahydropyrido-[2,1-b][1,3]oxazine (37a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 3.87 and 3.31 (ABq, *J* = 11.2 Hz, 2H, $OC\underline{H}_2$), 3.46 (dd, *J* = 9.6, 2.8 Hz, 1H, -NC$\underline{H}$O-), 2.82 (s, 1H, NC$\underline{H}$Ph), 2.66 (dd, *J* = 8.8, 2.0 Hz, 1H, $NC\underline{H}_2$), 1.49 (m, 1H, $NC\underline{H}_2$), 1.60 (m, 6H, $(CH_2)_3$), 1.63 and 0.23 (ABq, *J* = 14.0 Hz, 2H, $TMSC\underline{H}_2$), 0.64 (s, 3H, CH_3), 0.00 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) 137.71 (s), 126.27 (d), 126.83 (d), 94.29 (d), 78.69 (d), 76.36 (t), 50.05 (t), 36.30 (s), 31.18 (t), 24.35 (t), 22.60 (t), 22.37 (q), 19.40 (t), 0.00 (q); IR (thin film, NaCl) 3085, 2950, 2711, 1602, 1583, 1494, 1229, 1007, 842 cm^{-1}; LRMS $C_{18}H_{21}N + H^+$, calcd. m/z 318.22, observed m/z 318.4.

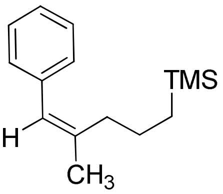
Data for (3*R*,4*S*,9a*S*)-3-methyl-4-phenyl-3-((trimethylsilyl)methyl)octahydropyrido-[2,1-b][1,3]oxazine (37b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 3.91 and 3.44 (ABq, *J* = 10.8 Hz, 2H, $OC\underline{H}_2$), 3.49 (dd, *J* = 10.0, 2.8 Hz, 1H, -NC$\underline{H}$O-), 2.85 (s, 1H, NC$\underline{H}$Ph), 2.60 (dd, *J* = 8.8, 2.0 Hz, 1H, $NC\underline{H}_2$), 1.48 (m, 1H, $NC\underline{H}_2$), 1.60 (m, 6H, $(CH_2)_3$), 1.31 (s, 3H, CH_3), 0.40 (ABq, 2H, $TMSC\underline{H}_2$), 0.00 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) 137.73 (s), 125.75 (d), 93.69 (d), 78.33 (d), 77.88 (t), 50.11 (t), 36.59 (s), 31.07 (t), 25.52 (t), 24.20 (t), 22.38 (t), 19.63 (q), 0.00 (q); IR (thin film, NaCl) 3060, 2948, 1601, 1493, 1451, 1249, 1136, 1023, 838 cm^{-1}; LRMS (M + H$^+$); calcd for $C_{18}H_{21}N$, 318.22; observed, 318.4.



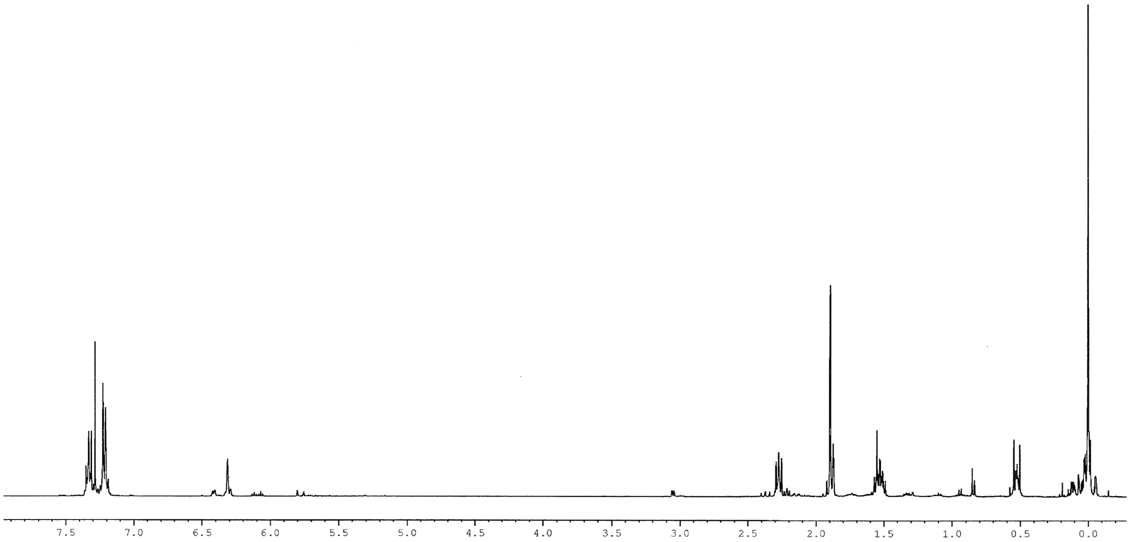
13

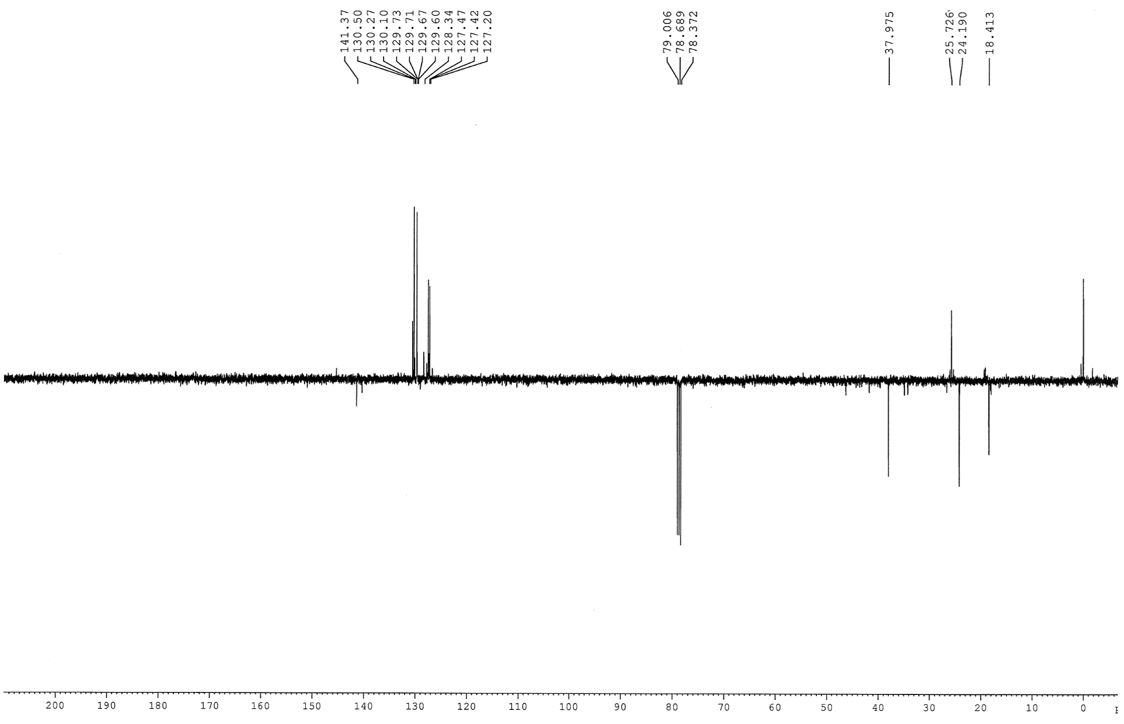


^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **13** (CDCl$_3$)

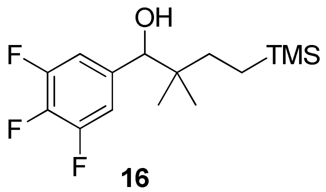


14

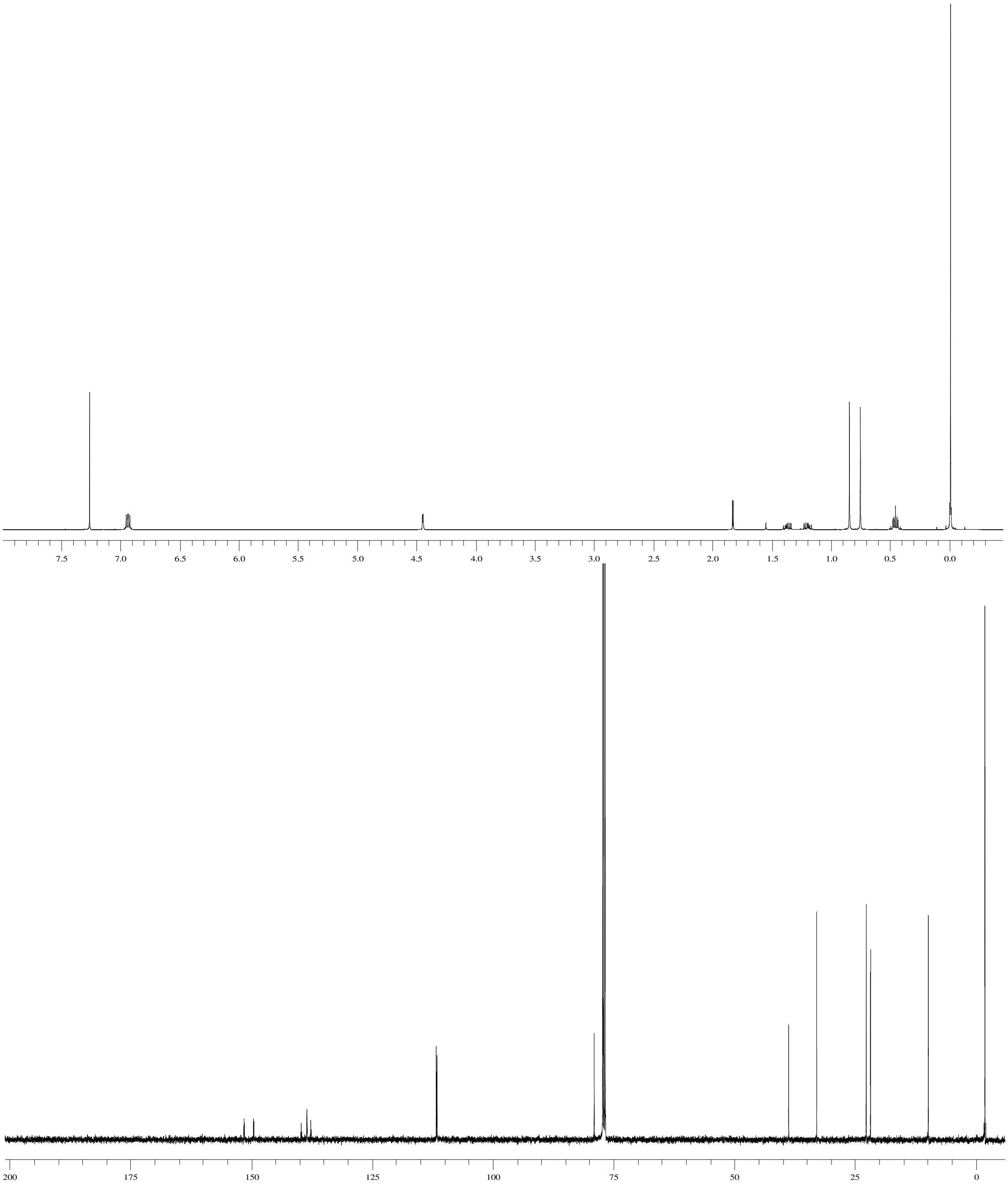




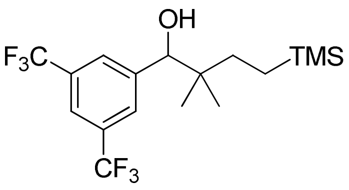
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **14** (CDCl$_3$) (contains a little impurities)



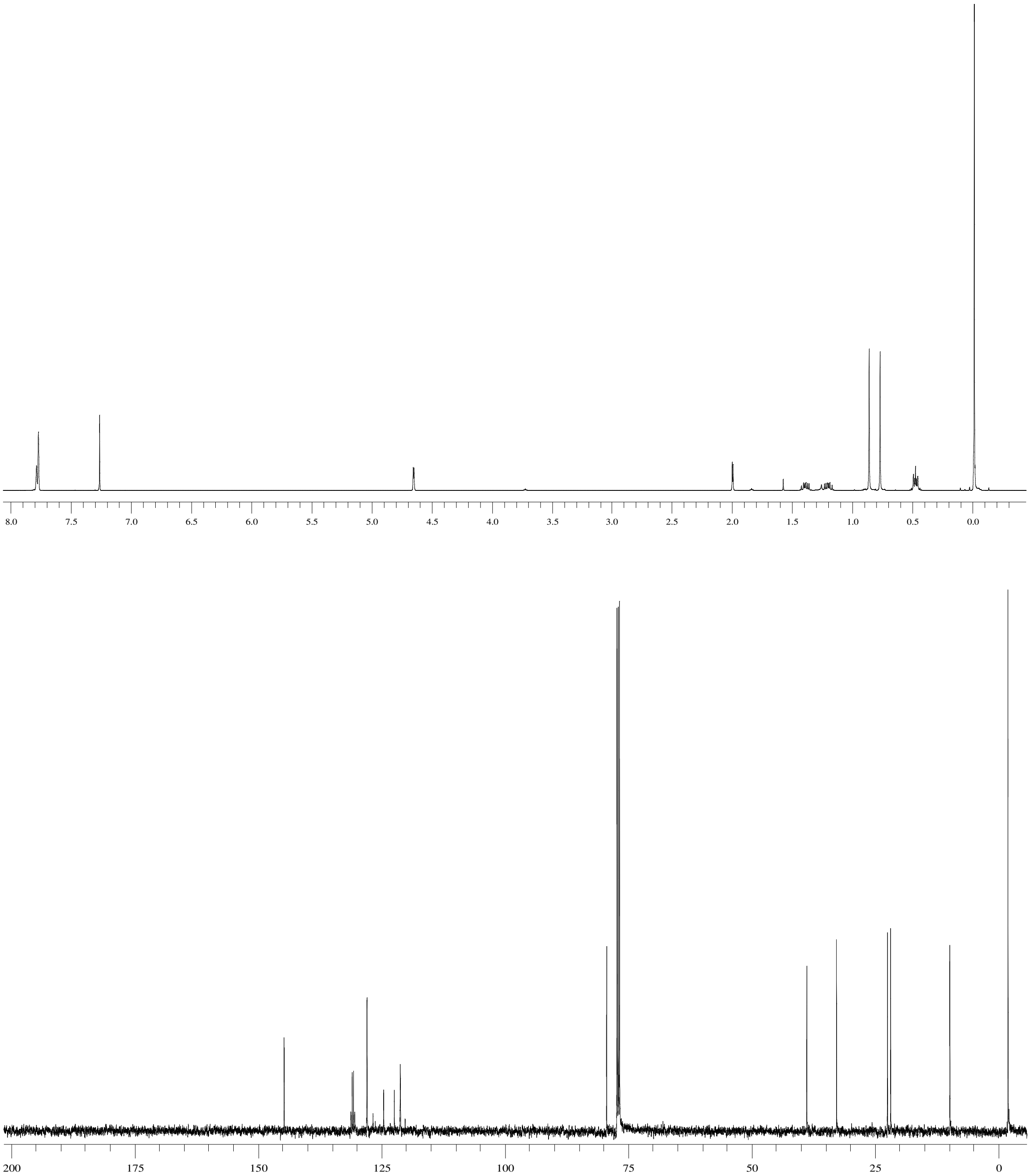
16



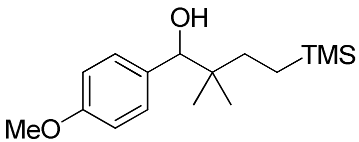
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **16** ($CDCl_3$)



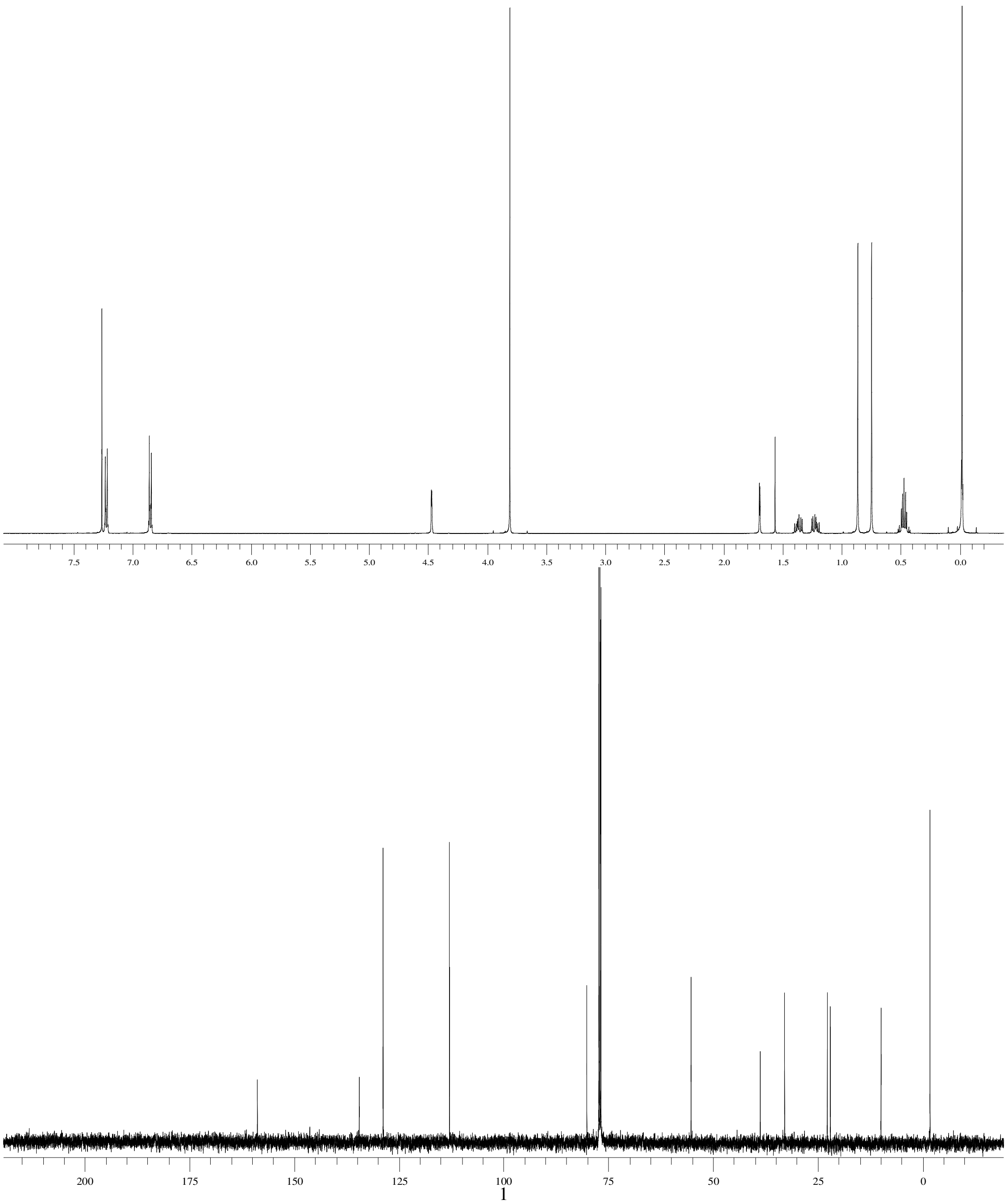
18



^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **18** (CDCl$_3$)

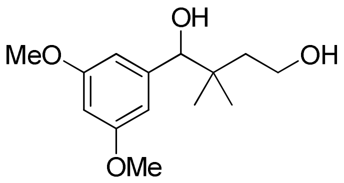


20

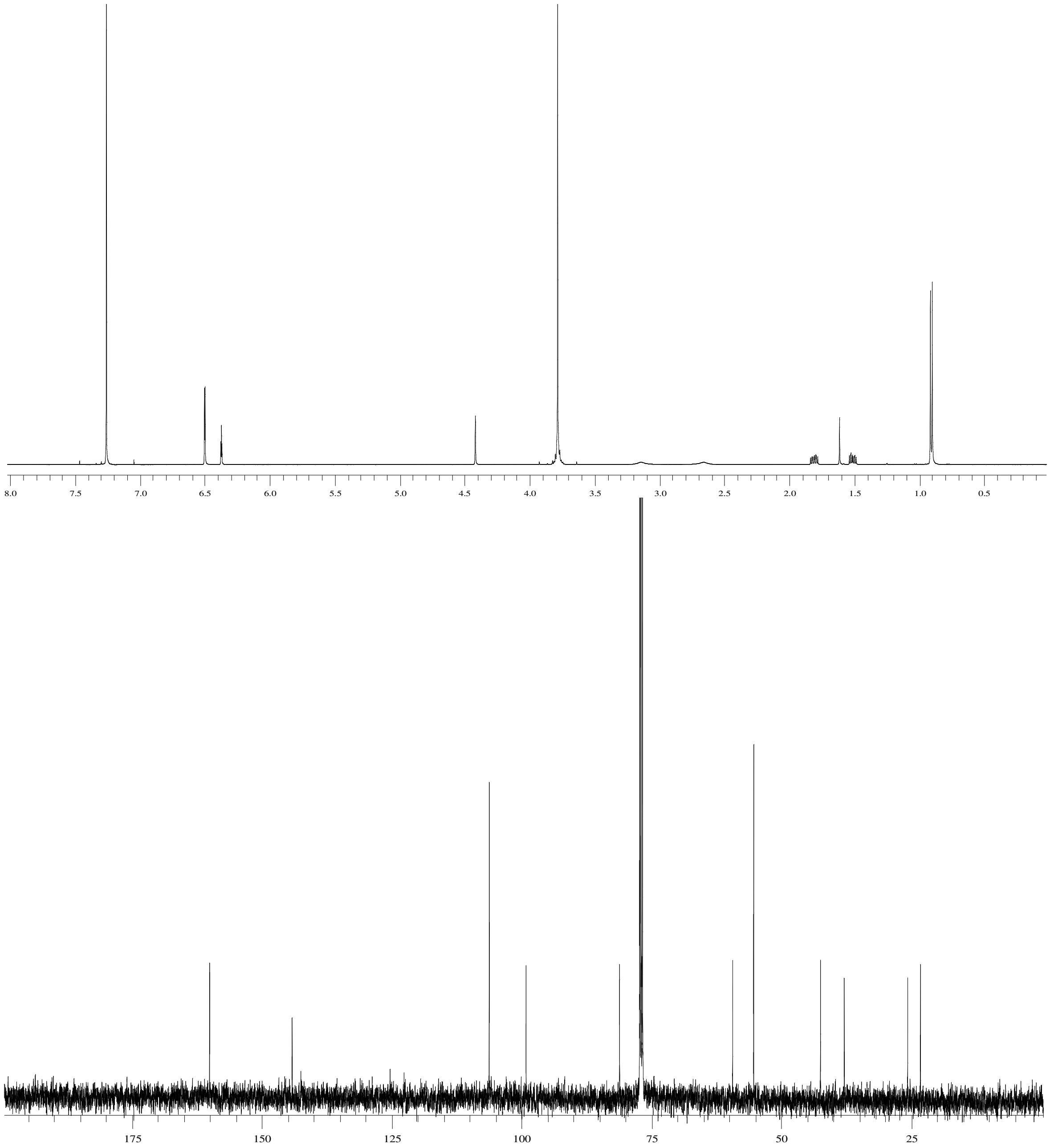


1

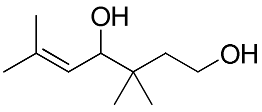
(500 MHz) and ^{13}C (126 MHz) of compound **20** ($CDCl_3$)



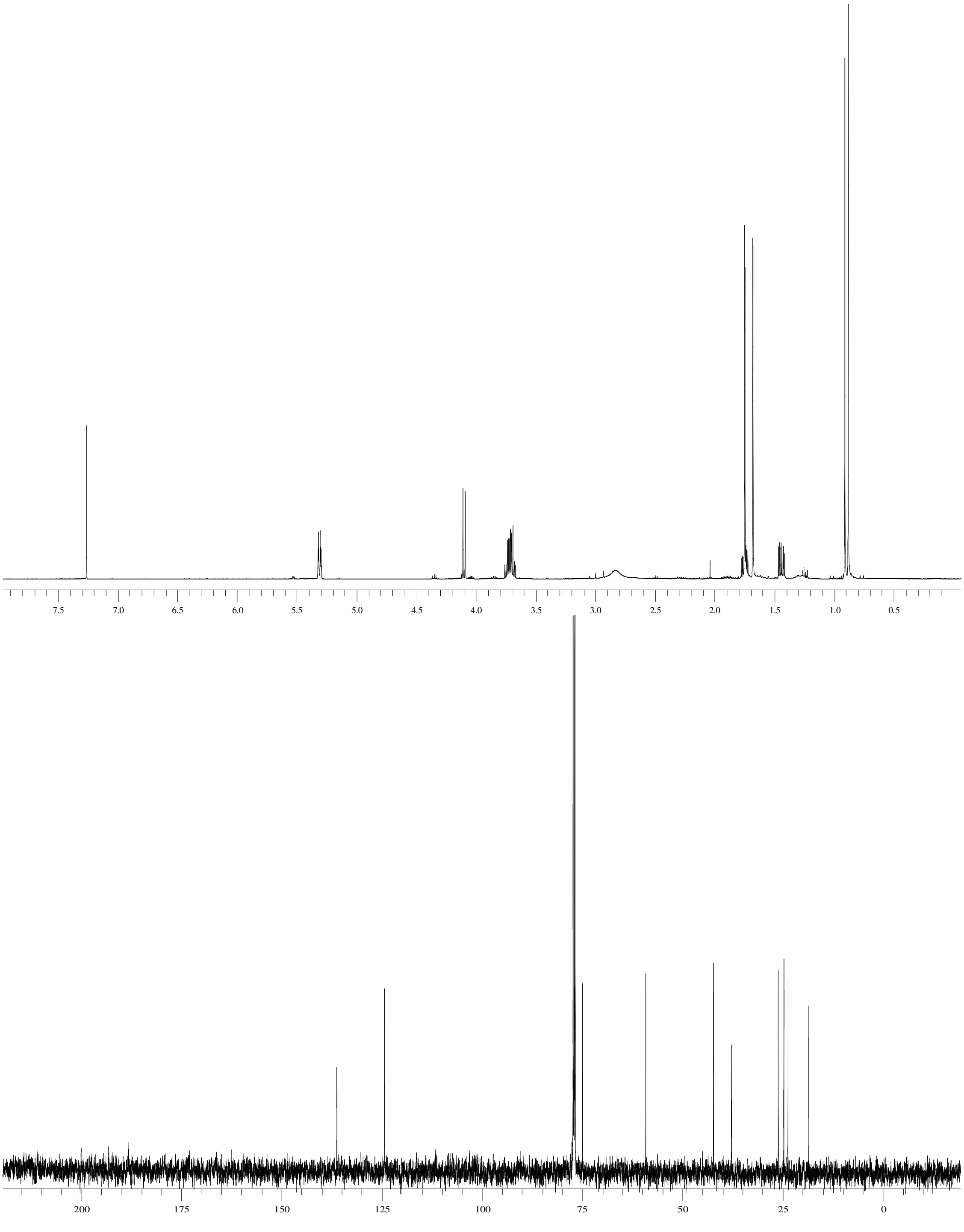
23



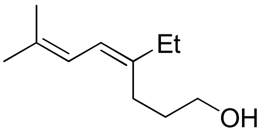
(500 MHz) and ^{13}C (126 MHz) of compound **23** (CDCl$_3$)



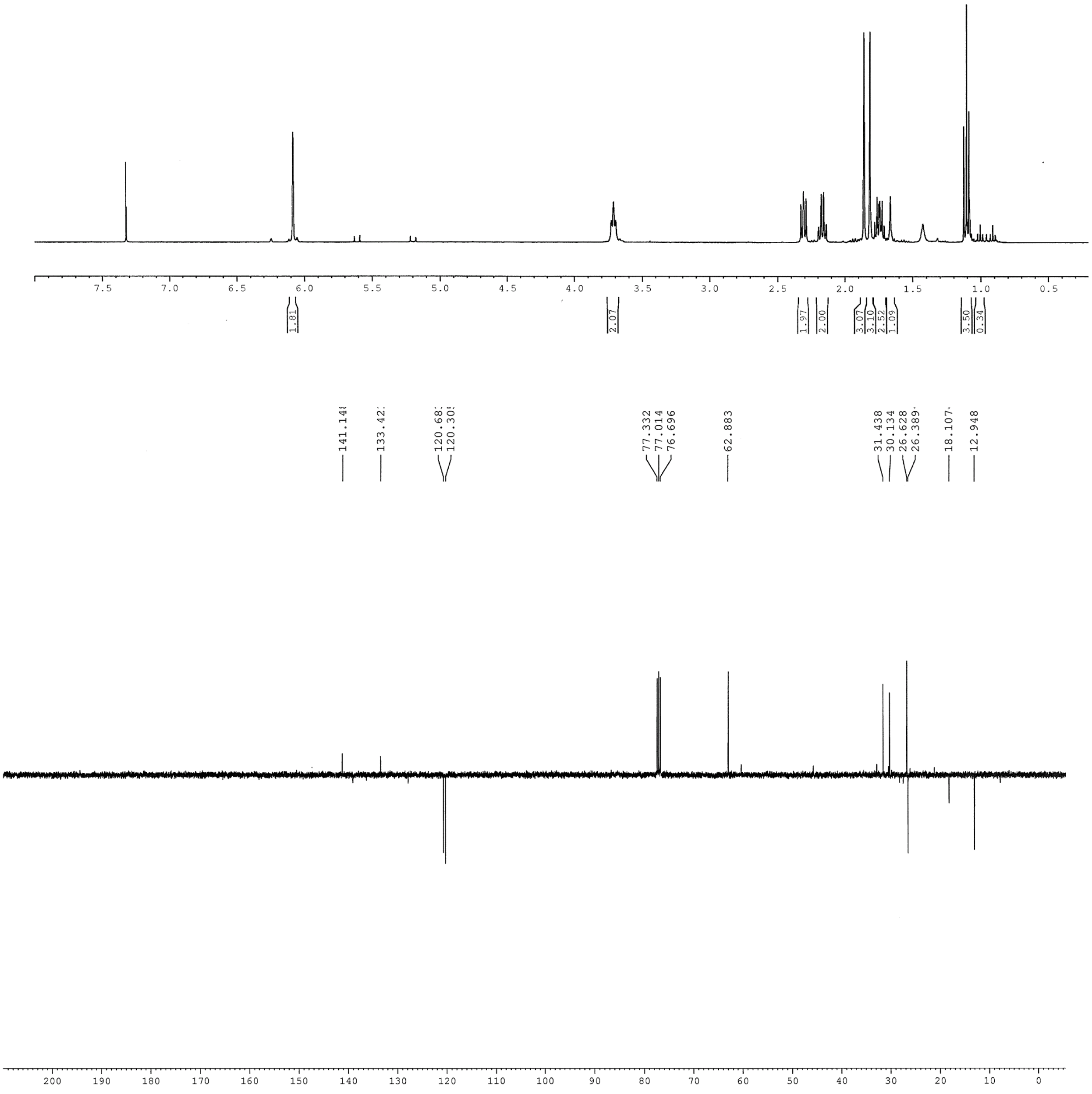
25



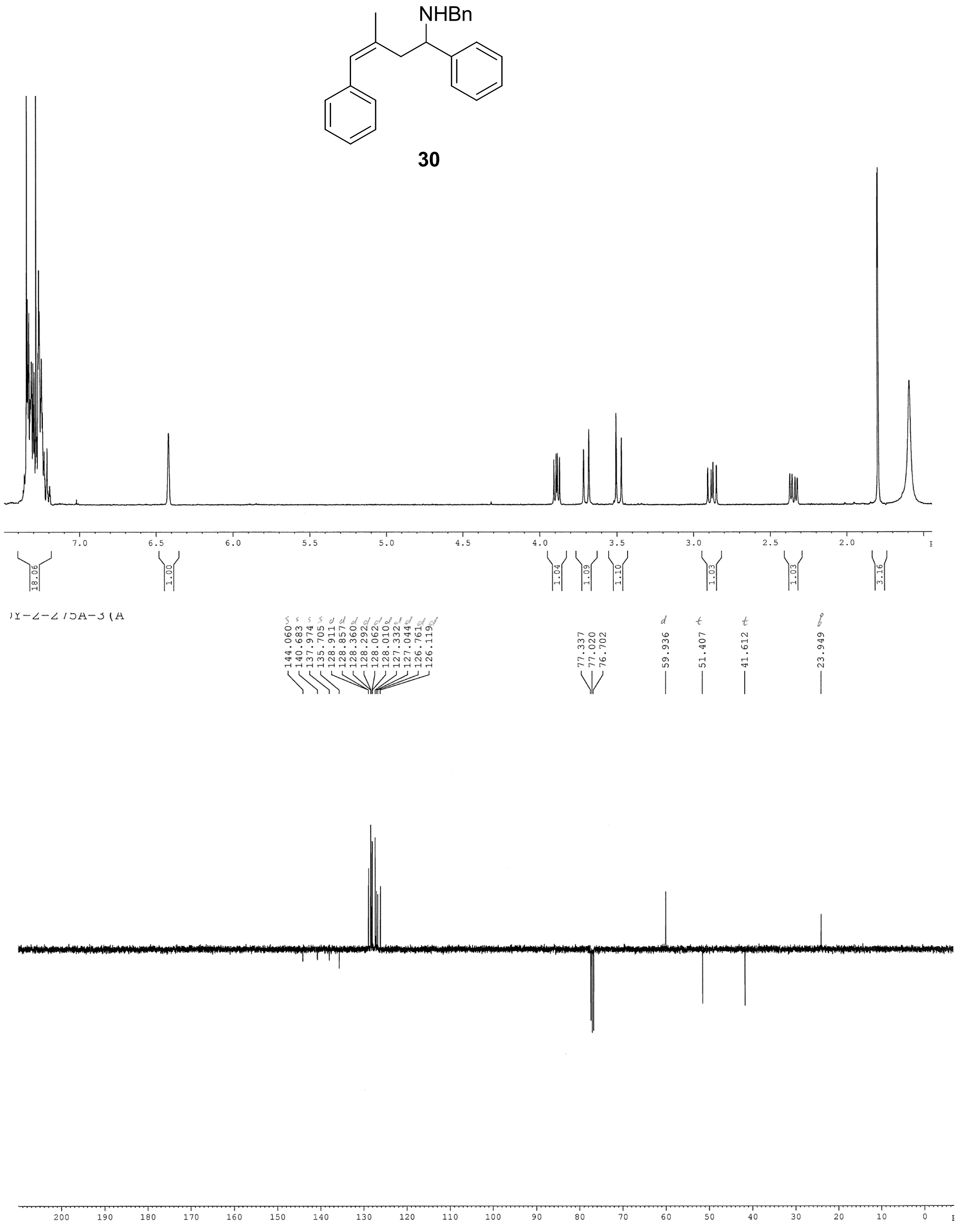
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **25** ($CDCl_3$)



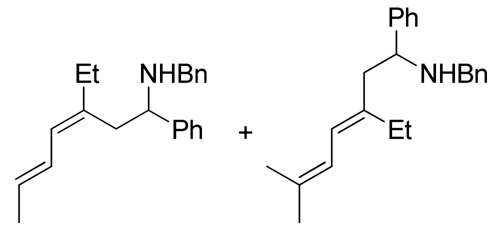
27



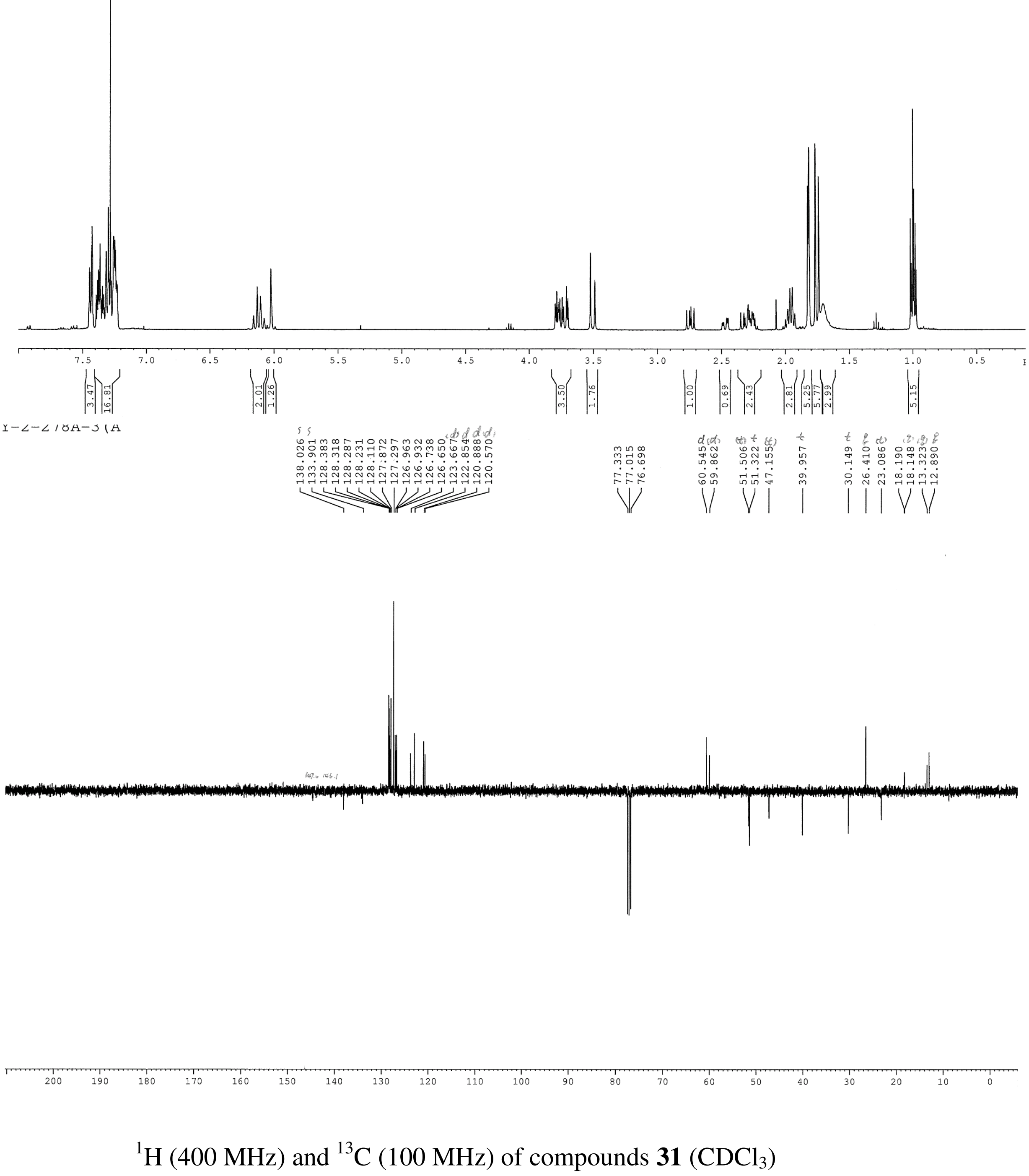
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **27** ($CDCl_3$)



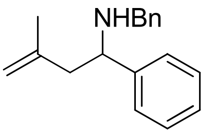
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **30** (CDCl$_3$)



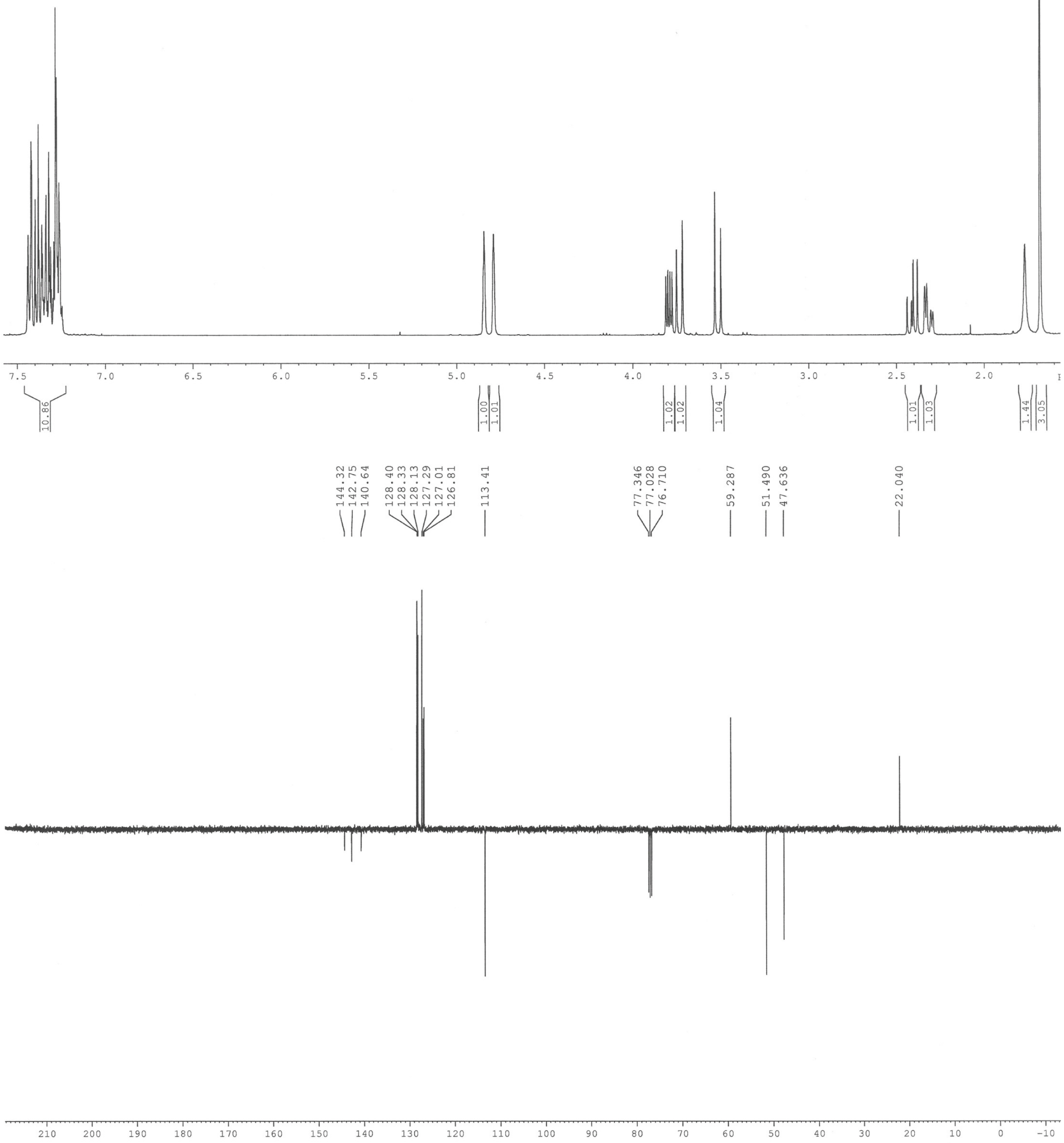
31 (1:0.7 mixture)



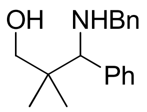
^{1}H (400 MHz) and ^{13}C (100 MHz) of compounds **31** (CDCl$_3$)



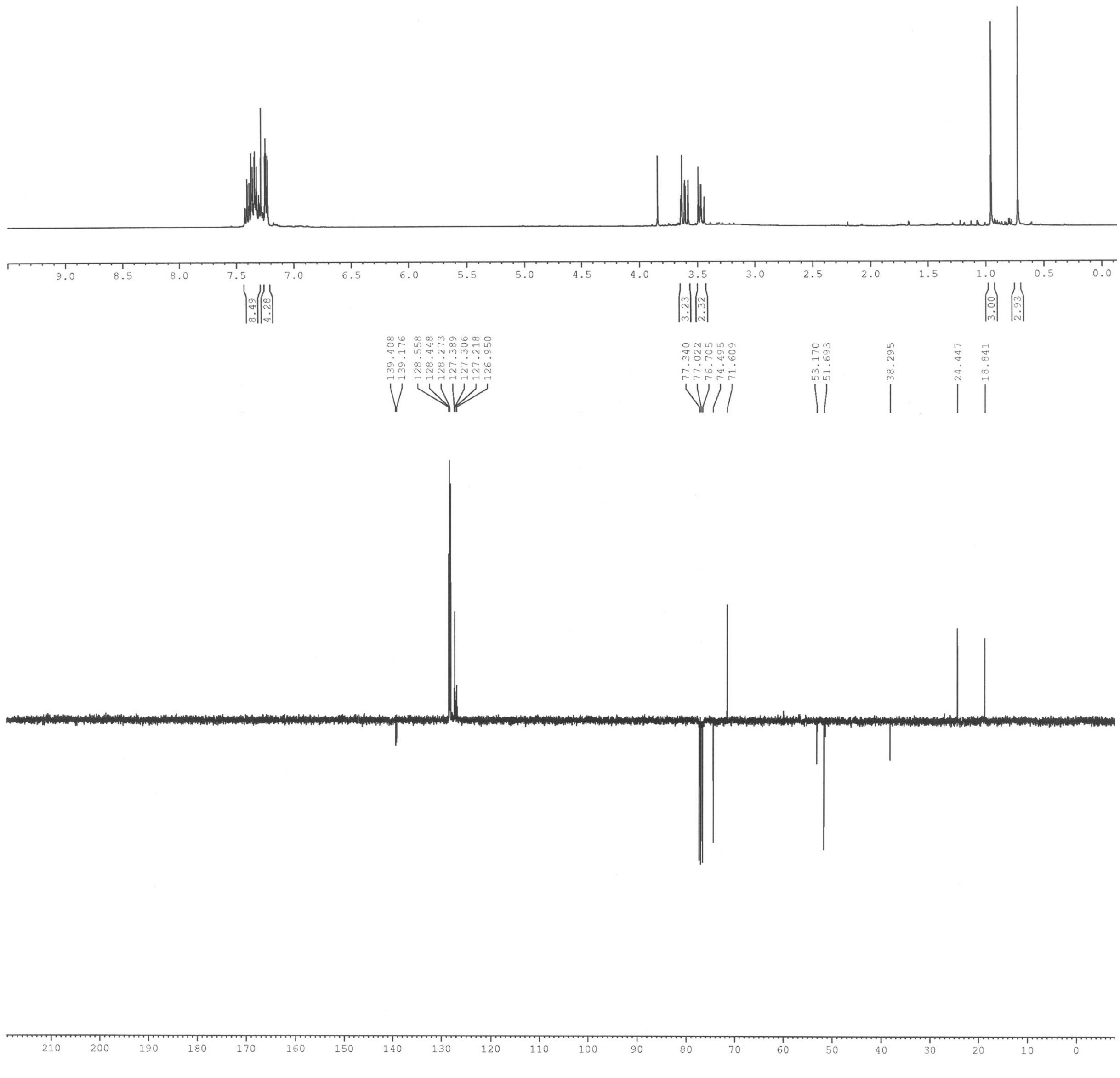
33a



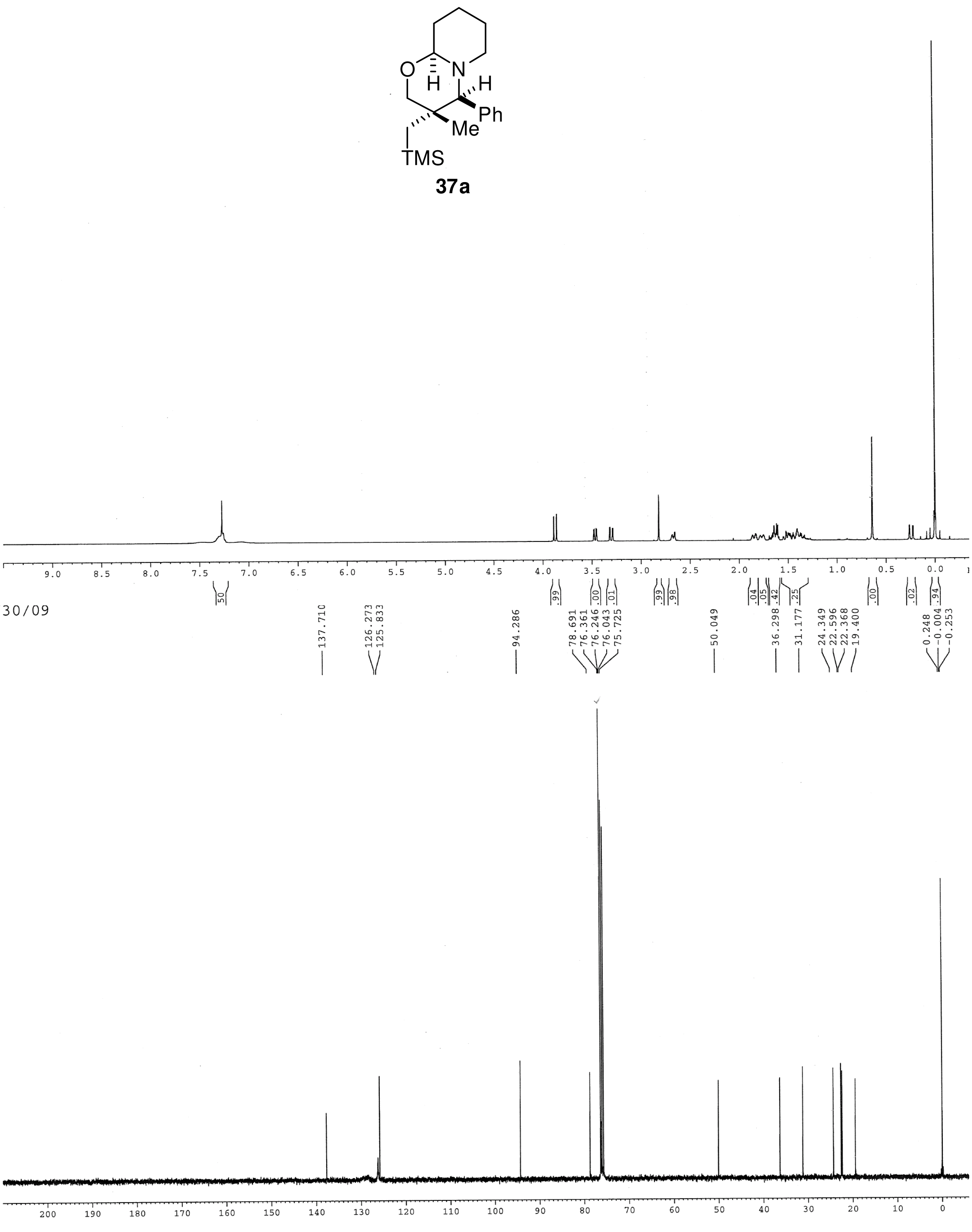
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **33a** (CDCl$_3$)



34a

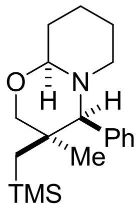


^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **34a** ($CDCl_3$)

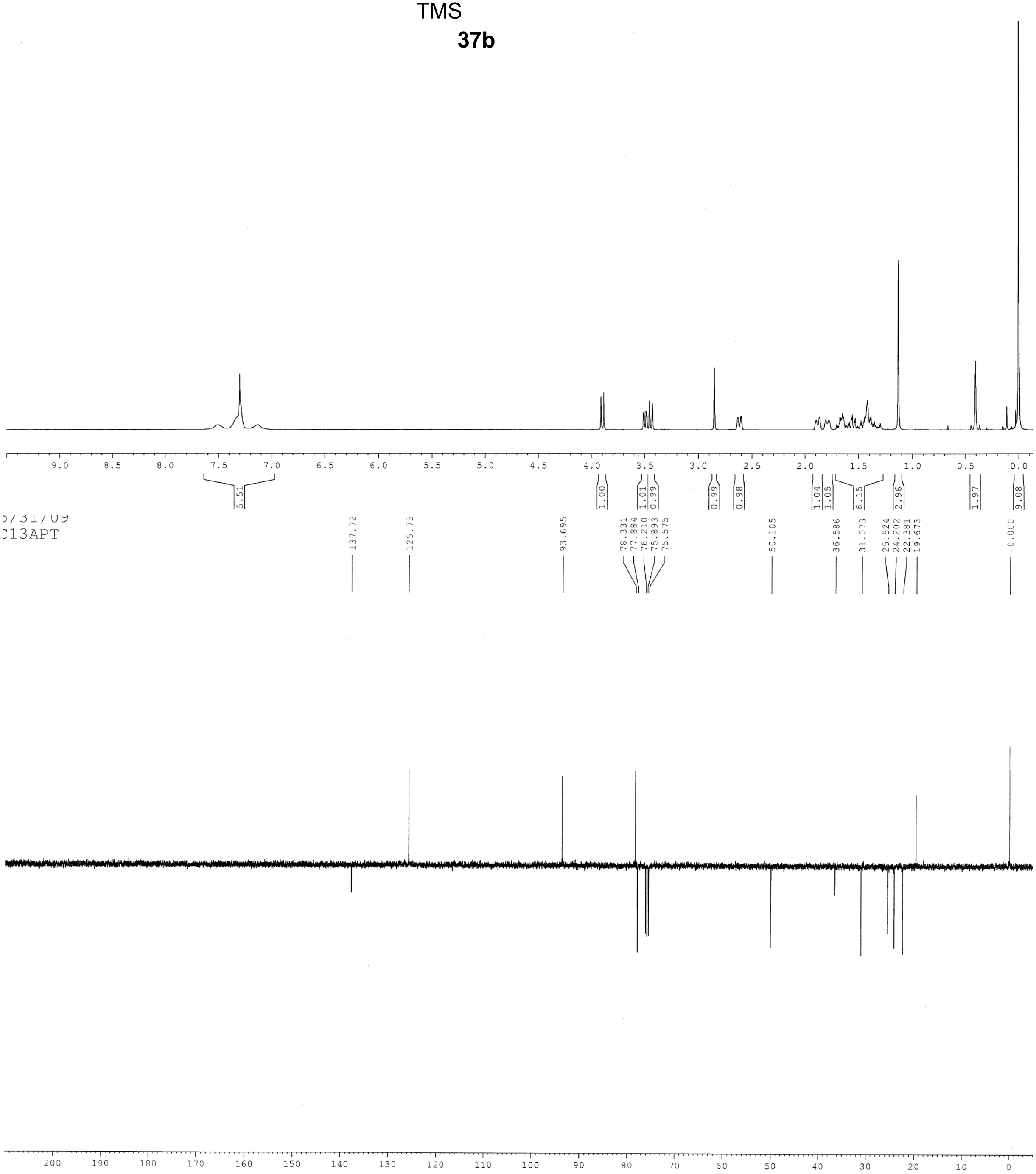


37a

^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **37a** ($CDCl_3$)



37b



^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **37b** (CDCl$_3$)