Supporting Information

Synthesis of Highly Substituted Indolines and Indoles via Intramolecular [4+2] Cycloaddition of Ynamides and Conjugated Enynes

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General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and tetrahydrofuran were purified by pressure filtration through activated alumnia. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Pyridine was distilled under argon from calcium hydride and degassed (prior to use in N-alkynylation reactions) by argon bubbling for ca. 20 min. Piperidine, triethylamine, and hexamethyldisilazane were distilled under argon from calcium hydride. Chlorotrimethylsilane, chlorotriisopropylsilane, (trifluoromethanesulfonyl)triisopropylsilane, and trifluoromethanesulfonyl anhyride were distilled under argon from phosphorous pentoxide. Methyl chloroformate was distilled under argon. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. *N*-Bromosuccinimide was recrystallized from boiling water. 2-Bromopropene was passed through a pad of alumina in a disposable pipette prior to use.

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with an Inova 500 spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 Telsa Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.

Part I. Experimental Procedures for [4+2] Cycloadditions

***N*-(*p*-Toluenesulfonyl)-5-methyl-7-(trimethylsilyl)indoline (15).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **6** (0.235 g, 0.654 mmol), BHT (0.433 g, 1.96 mmol), and 13 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 210 °C for 75 min and then allowed to cool to rt. Concentration afforded 0.706 g of a brown oil. Column chromatography on 70 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.131 g (56%) of indoline **15** as a white solid: mp 122-126 °C; IR ($CHCl_3$) 2955, 1598, 1349, and 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 6.83 (s, 1H), 3.91 (t, J = 7.3 Hz, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 2.00 (t, J = 7.3 Hz, 2H), and 0.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 143.9, 136.6, 135.8, 135.4, 134.5, 134.2, 129.4, 127.9, 125.8, 51.6, 28.3, 21.8, 21.4, and 1.1; Anal. Calcd for $C_{19}H_{25}NO_2SSi$: C, 63.47; H, 7.01; N, 3.90. Found: C, 63.61; H, 7.23; N, 3.86.

***N*-(*p*-Toluenesulfonyl)-5-methylindoline (16).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **7** (0.190 g, 0.661 mmol), BHT (0.437 g, 1.98 mmol), and 13 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 210 °C for 75 min and then allowed to cool to rt. Concentration afforded 0.659 g of a brown oil. Column chromatography on 80 g of silica gel (gradient elution with 2-5% EtOAc-hexanes) provided 0.096 g (51%) of indoline **16** as a white solid: mp 75-77 °C; IR (CH_2Cl_2) 3055, 2924, 1598, 1485, 1353, and 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 3.89 (t, J = 8.4 Hz, 2H), 2.81 (t, J = 8.4 Hz, 2H), 2.36 (s, 3H), and 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 139.7, 134.0, 133.6, 132.2, 129.7, 128.3, 127.4, 125.9, 115.1, 50.2, 28.0, 21.7, and 21.0; GC-MS *m/z*: 287 (M^+).

***N*-(Trifluoromethanesulfonyl)-5-methyl-7-(trimethylsilyl)indoline (17).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **8** (0.146 g, 0.433 mmol), BHT (0.286 g, 1.30 mmol), and 9 mL of toluene. The solution was degassed by

three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 5 h and then allowed to cool to rt. Concentration afforded 0.422 g of a dark brown oil. Column chromatography on 40 g of silica gel (elution with pentanes) provided 0.100 g (68%) of indoline **17** as a white solid: mp 106-109 °C; IR ($CHCl_3$) 2956, 2865, 1583, 1443, 1396, and 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.11 (s, 1H), 4.22 (app br s, 2H), 3.08 (app br s, 2H), 2.37 (s, 3H), and 0.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 136.9, 135.9, 135.1, 132.6, 126.5, 120.9 (q, J_{CF} = 327 Hz), 53.1, 29.3, 21.3, and 1.0; GC-MS *m/z*: 337 (M^+); Anal. Calcd for $C_{13}H_{18}F_3NO_2SSi$: C, 46.27; H, 5.38; N, 4.15. Found: C, 46.41; H, 5.51; N, 4.14.

***N*-(Trifluoromethanesulfonyl)-5-methylindoline (18).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **9** (0.181 g, 0.682 mmol), BHT (0.452 g, 2.05 mmol), and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 5 h and then allowed to cool to rt. Concentration afforded 0.918 g of a dark brown oil. Column chromatography on 20 g of silica gel (gradient elution with 0.5-1% EtOAc-hexanes) provided 0.102 g (56%) of indoline **18** as a pale yellow oil with spectral characteristics consistent with those previously reported:[1] IR (neat) 2926, 2865, 1602, 1488, 1399 and 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 4.21 (t, J = 8.4 Hz, 2H), 3.19 (t, J = 8.4 Hz, 2H), and 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 135.1, 131.5, 128.6, 126.3, 120.5 (q, J_{CF} = 324 Hz), 114.3, 51.6, 28.2, and 21.0; GC-MS *m/z*: 265 (M^+).

***N*-(Methoxycarbonyl)-5-methyl-7-(trimethylsilyl)indoline (19).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **5** (0.205 g, 0.778 mmol), BHT (0.171 g, 0.776 mmol), and 16 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 16 h and then allowed to cool to room temperature. Concentration afforded 0.377 g of a pale brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0-3% EtOAc-hexanes) provided 0.152 g (74%) of indoline **19** as a white solid: mp 65-67 °C; IR ($CHCl_3$) 3017, 2861, 1720, 1607, 1583, and 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.08 (s, 1H), 4.16 (t, J = 7.7 Hz, 2H), 3.83 (s, 3H), 2.99 (t, J = 7.7 Hz, 2H), 2.38 (s,

[1] Padwa, A.; Rashatasakhan, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 5139.

3H), and 0.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 144.8, 134.5, 133.4, 129.2, 128.6, 126.1, 52.8, 50.0, 29.2, 21.1, and 0.4; GC-MS *m/z*: 263 (M^+); Anal. Calcd for $C_{14}H_{21}NO_2Si$: C, 63.84; H, 8.04; N, 5.32. Found: C, 64.10; H, 7.90; N, 5.40.

***N*-(Methoxycarbonyl)-5-methylindoline (20).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **10** (0.190 g, 0.994 mmol), BHT (0.219 g, 0.994 mmol), and 20 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 210 °C for 2 h and then allowed to cool to rt. Concentration afforded 0.414 g of a pale brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0-3% EtOAc-hexanes) provided 0.134 g (71%) of indoline **20** as a pale yellow solid: mp 55-58 °C; IR (film) 2952, 2919, 1710, 1613, 1498, and 1450 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 6.97 (br s, 1H), 6.94 (s, 1H), 3.91 (br s, 2H), 3.79 (br s, 3H), 3.02 (t, J =8.7 Hz, 2H), and 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 140.2, 131.9, 130.8, 127.7, 125.2, 114.2, 52.2, 47.2, 27.4, and 20.8; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.34; H, 7.13; N, 7.02.

***N*-(Methoxycarbonyl)-5-methyl-7-[2-(trimethylsilyl)ethynyl]indoline (21).** A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with ynamide **11** (0.182 g, 0.633 mmol), BHT (0.140 g, 0.635 mmol), and 13 mL of toluene. The septum was replaced with a glass stopper and the solution was heated at reflux for 14 h. The reaction mixture was allowed to cool to room temperature and then concentrated to afford 0.336 g of a dark brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.125 g (69%) of indoline **21** as a white solid: mp 77-81 °C; IR (CH_2Cl_2) 2957, 2151, 1708, 1588, and 1443 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.97 (s, 1H), 4.11 (t, J = 7.9 Hz, 2H), 3.81 (s, 3H), 2.96 (t, J = 7.9 Hz, 2H), 2.26 (s, 3H), and 0.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 140.8, 134.7, 133.5, 132.8, 126.2, 112.4, 103.0, 98.2, 52.4, 50.6, 29.0, 20.7, and 0.2; Anal. Calcd for $C_{16}H_{21}NO_2Si$: C, 66.86; H, 7.36; N, 4.87. Found: C, 66.43; H, 7.63; N, 4.56.

***N*-(Methoxycarbonyl)-5-methyl-7-[3-(triisopropylsiloxy)-1-propynyl]indoline (22).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and reflux condenser fitted with an argon inlet adapter was charged with ynamide **12** (0.287 g, 0.715 mmol), BHT (0.158 g, 0.717 mmol),

and 14 mL of toluene. The septum was replaced with a glass stopper and the solution was heated at reflux for 14 h. The reaction mixture was allowed to cool to room temperature and then concentrated to afford 0.450 g of a red oil. Column chromatography on 100 g of silica gel (gradient elution with 0-15% EtOAc-hexanes) provided 0.123 g (43%) of indoline **22** as a beige solid: mp 53-55 °C; IR (CH_2Cl_2) 2944, 2865, 2235, 1708, 1592, and 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.95 (s, 1H), 4.62 (s, 2H), 4.08 (t, J = 7.9 Hz, 2H), 3.82 (s, 3H), 2.94 (t, J = 7.9 Hz, 2H), 2.26 (s, 3H), 1.14 (sept, J = 6.1 Hz, 3H), and 1.10 (d, J = 6.1 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 140.8, 134.7, 133.5, 132.4, 125.8, 112.4, 92.1, 82.5, 52.7, 52.5, 50.6, 29.0, 20.8, 18.1, and 12.1; Anal. Calcd for $C_{23}H_{35}NO_3Si$: C, 68.78; H, 8.78; N, 3.49. Found: C, 69.02; H, 9.05; N, 3.40.

***N*-(Methoxycarbonyl)-9-[3-(triisopropylsiloxy)-3-methyl-1-butynyl]-5,6,7,8-tetrahydrobenzo[*f*]indoline (23).** A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **13** (0.216 g, 0.460 mmol), BHT (0.101 g, 0.458 mmol), and 9 mL of toluene. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature and concentrated to afford 0.322 g of a pale brown oil. Column chromatography on 60 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.165 g (76%) of indoline **23** as a pale yellow oil: IR (neat) 2941, 2864, 2219, 1709, 1606, and 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 4.09 (t, J = 7.6 Hz, 2H), 3.81 (s, 3H), 2.92 (t, J = 7.6 Hz, 2H), 2.88 (app t, J = 6.1 Hz, 2H), 2.71 (app t, J = 6.1 Hz, 2H), 1.74-1.84 (m, 4H), 1.67 (s, 6H), 1.15 (sept, J = 7.0 Hz, 3H), and 1.08 (d, J = 7.0 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 142.1, 138.4, 133.3, 131.6, 125.2, 113.2, 104.2, 78.7, 67.2, 52.8, 51.2, 33.6, 29.9, 29.2, 28.5, 23.3, 23.0, 18.5, and 13.2; Anal. Calcd for $C_{28}H_{43}NO_3Si$: C, 71.59; H, 9.23; N, 2.98. Found: C, 71.32; H, 9.42; N, 3.02.

***N*-(Methoxycarbonyl)-7-(3-hydroxy-3-methyl-1-butynyl)-6-methoxycarbonyl-5-methylindoline (24).** A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **14** (0.316 g, 0.954 mmol), BHT (0.210 g, 0.953 mmol), and 19 mL of toluene. The reaction mixture was heated at reflux for 5 h and then allowed to cool to room temperature and concentrated to afford 0.553 g of a brown oil. Column chromatography on 80 g of silica gel (gradient elution with 30-45% EtOAc-hexanes) provided 0.125 g (40%) of indoline **24** as a pale yellow solid: mp 118-120 °C; IR (film) 3451, 2981, 2954, 2226, 1727, 1710, 1601, 1584, and 1442 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 4.05 (t, J = 7.9 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.28 (s,

1H), 2.93 (t, J = 7.9 Hz, 2H), 2.21 (s, 3H), and 1.52 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 154.3, 141.4, 136.2, 135.9, 130.9, 126.5, 110.0, 102.6, 77.6, 65.4, 52.9, 52.4, 50.6, 31.3, 28.9, and 19.2; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{21}NO_5$, 354.1312; found, 354.1296.

***N*-(Methoxycarbonyl)-4-methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indoline (30).**

Thermal Cycloaddition. A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **25** (0.325 g, 1.12 mmol), BHT (0.249 g, 1.13 mmol), and 23 mL of toluene. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature and concentrated to afford 0.581 g of a pale yellow solid. Column chromatography on 80 g of silica gel (gradient elution with 5-15% EtOAc-hexanes) provided 0.312 g (96%) of indoline **30** as an off-white solid.

Lewis Acid-Promoted Cycloaddition. A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **25** (0.101 g, 0.349 mmol) and 7 mL of CH_2Cl_2 and cooled at 0 °C while 0.87 mL of Me_2AlCl solution (1.0 M in hexanes, 0.87 mmol) was added via syringe over 1 min. The resulting pale orange solution was stirred at 0 °C for 1 h, and then the ice bath was removed and the solution was stirred at rt for 2 h. The reaction mixture was diluted with 70 mL of Et_2O, 20 mL of satd $NaHCO_3$ solution, and 30 mL of water. The aqueous layer was separated and extracted with three 25-mL portions of Et_2O, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.108 g of a yellow oil. Two successive purifications by column chromatography on 20 g of silica gel (gradient elution with 5-20% EtOAc-hexanes) provided 0.078 g (78%) of indoline **30** as an off-white solid: mp 108-110 °C; IR (film) 2931, 1721, 1712, 1603, 1469, and 1441 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 3.97 (br s, 2H), 3.88 (s, 3H), 3.82 (br s, 3H), 3.17 (t, J = 8.4 Hz, 2H), 2.80 (m, 4H), and 1.76 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 153.3, 140.4, 137.4, 130.0, 128.7, 128.3, 117.3, 52.3, 51.5, 47.2, 30.4, 27.6, 27.2, 23.1, and 22.6; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}NO_4$, 290.1387; found, 290.1379.

***N*-(tert-Butoxycarbonyl)-4-methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indoline (31).** A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **26** (0.212 g, 0.640 mmol), BHT (0.141 g, 0.640 mmol), and 13 mL of toluene. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature and concentrated to afford 0.347 g of a yellow oil. Column chromatography on 80 g of silica gel (gradient

elution with 0-2% EtOAc-hexanes) provided 0.192 g (91%) of indoline **31** as a white solid: mp 78-81 °C; IR (film) 2932, 1723, 1704, 1603, and 1468 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 3.90 (br s, 2H), 3.85 (s, 3H), 3.11 (t, J = 8.4 Hz, 2H), 2.76 (m, 4H), 1.73 (m, 4H), and 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 152.6, 140.8, 137.5, 129.7, 128.9, 128.5, 117.6, 80.5, 51.7, 47.7, 30.6, 28.5, 27.6, 27.3, 23.3, and 22.8; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{25}NO_4$, 354.1676; found, 354.1683.

***N*-(Methoxycarbonyl)-6-methyl-4-(trimethylsilyl)indoline (32).** A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with the ynamide **27** (0.180 g, 0.683 mmol), BHT (0.151 g, 0.685 mmol), and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles, and the tube was then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 16 h and then allowed to cool to room temperature. Concentration afforded 0.334 g of a pale brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0-2% EtOAc-hexanes) provided 0.155 g (86%) of indoline **32** as a white solid: mp 89-91 °C; IR (film) 2954, 1716, 1596, 1569, 1450, and 1420 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 6.94 (s, 1H), 4.02 (br s, 2H), 3.85 (br s, 3H), 3.14 (t, J = 8.5 Hz, 2H), 2.38 (s, 3H), and 0.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 142.2, 136.7, 135.4, 133.1, 128.8, 116.5, 52.5, 47.6, 28.4, 21.8, and –0.7; Anal. Calcd for $C_{14}H_{21}NO_2Si$: C, 63.84; H, 8.04; N, 5.32. Found: C, 63.82; H, 8.16; N, 5.24.

***N*-(Methoxycarbonyl)-4-(methoxycarbonyl)-6-methylindoline (33).** A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ynamide **28** (0.132 g, 0.530 mmol), BHT (0.117 g, 0.531 mmol), and 11 mL of toluene. The reaction mixture was heated at reflux for 30 h and then allowed to cool to room temperature and concentrated to afford 0.252 g of a pale red solid. Column chromatography on 40 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) provided 0.126 g (95%) of indoline **33** as a white solid: mp 102-105 °C; IR (film) 2957, 1724, 1712, 1609, 1487, and 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.44 (s, 1H), 4.02 (t, J = 8.5 Hz, 2H), 3.89 (s, 3H), 3.83 (br s, 3H), 3.42 (t, J = 8.5 Hz, 2H), and 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 153.7, 143.9, 137.8, 131.2, 126.0, 124.4, 119.4, 52.6, 51.8, 47.9, 28.5, and 21.6; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}NO_4$, 250.1074; found, 250.1071.

***N*-(Methoxycarbonyl)-4-[3-(triisopropylsiloxy)-3-methyl-1-butynyl]-6-methylindoline (34).** A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was

charged with ynamide **29** (0.203 g, 0.472 mmol), BHT (0.104 g, 0.472 mmol), and 9 mL of toluene. The reaction mixture was heated at reflux for 30 h and then allowed to cool to room temperature and concentrated to afford 0.306 g of a pale brown oil. Column chromatography on 35 g of silica gel (elution with toluene) provided 0.170 g (84%) of indoline **34** as a pale yellow oil: IR (neat) 2943, 2865, 2218, 1722, 1589, 1488, and 1446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 6.80 (s, 1H), 4.01 (br s, 2H), 3.82 (s, 3H), 3.09 (t, J = 8.5 Hz, 2H), 2.32 (s, 3H), 1.62 (s, 6H), 1.19 (sept, J = 7.3 Hz, 3H), and 1.11 (d, J = 7.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 142.8, 137.8, 130.7, 126.0, 119.3, 115.6, 98.1, 80.2, 66.7, 52.6, 47.6, 33.6, 27.1, 21.7, 18.5, and 13.1; Anal. Calcd for $C_{25}H_{39}NO_3Si$: C, 69.88; H, 9.15; N, 3.26. Found: C, 70.04; H, 9.24; N, 3.36.

Part II. Experimental Procedures for Oxidation of Indolines to Indoles

***N*-(Methoxycarbonyl)-5-methylindole (35).** A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with indoline **20** (0.215 g, 1.12 mmol) and 3.7 mL of benzene. *o*-Chloranil (0.553 g, 2.25 mmol) was added in one portion and the resulting dark purple suspension was stirred at rt for 48 h. The reaction mixture was then filtered through a column of alumina (5 x 1.5 cm) with the aid of 500 mL of 10% EtOAc-hexanes. Concentration of the filtrate afforded 0.215 g of a dark red oil. Column chromatography on 100 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.180 g (85%) of indole **35** as a very pale red solid: mp 54-55 °C; IR (CH_2Cl_2) 3149, 2918, 1737, 1613, 1586, 1535, 1462, and 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.60 (br s, 1H), 7.40 (s, 1H), 7.21 (app dd, J = 1.2, 8.5 Hz, 1H), 6.57 (d, J = 3.7 Hz, 1H), 4.04 (s, 3H), and 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 133.4, 132.5, 130.7, 125.9, 125.5, 121.0, 114.7, 107.9, 53.7, and 21.3; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.98; H, 5.62; N, 7.36.

***N*-(Methoxycarbonyl)-4-methoxycarbonyl-6-methylindole (36).** A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **33** (0.029 g, 0.12 mmol) and 0.8 mL of benzene. *o*-Chloranil (0.057 g, 0.23 mmol) was added in one portion and the resulting dark purple suspension was stirred at rt for 160 h. The reaction mixture was then filtered through a column of silica gel (9 x 1.5 cm) with the aid of 300 mL of 10% EtOAc-hexanes.

Concentration of the filtrate afforded 0.047 g of an orange-red solid. Column chromatography on 40 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.022 g (77%) of indole **36** as a white solid: mp 81-82 °C; IR (film) 3136, 2957, 1742, 1714, 1612, 1582, 1528, and 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.83 (dd, J = 0.6, 1.5 Hz, 1H), 7.64 (d, J = 3.7 Hz, 1H), 7.23 (dd, J = 0.6, 3.7 Hz, 1H), 4.05 (s, 3H), 3.98 (s, 3H), and 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 151.5, 136.5, 134.3, 128.4, 127.2, 126.8, 121.8, 120.1, 108.8, 54.1, 52.1, and 21.9; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{13}NO_4$, 270.0737; found, 270.0733.

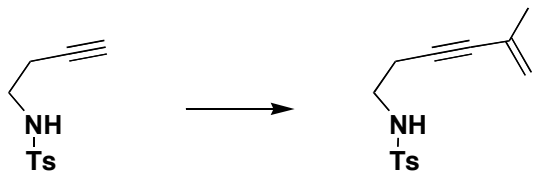
***N*-(Methoxycarbonyl)-4-methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indole (37).** A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **30** (0.172 g, 0.594 mmol) and 2.2 mL of benzene. *o*-Chloranil (0.292 g, 1.19 mmol) was added in one portion and the resulting dark purple suspension was stirred at rt for 120 h. The reaction mixture was then filtered through a column of silica gel (5 x 3 cm) with the aid of 750 mL of 10% EtOAc-hexanes. Concentration of the filtrate afforded 0.373 g of a dark red solid. Column chromatography on 40 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) provided 0.070 g (41%) of indole **37** as a white solid: mp 104-106 °C; IR (film) 3136, 2935, 2858, 1742, 1721, 1611, 1573, 1531, and 1444 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.54 (app d, J = 3.8 Hz, 1H), 6.75 (dd, J = 0.8, 3.8 Hz, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 3.05 (m, 2H), 2.96 (m, 2H), and 1.82 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 151.5, 135.2, 133.9, 133.2, 128.3, 126.0, 123.0, 118.3, 108.2, 54.0, 51.9, 31.1, 27.9, 23.4, and 22.9; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{17}NO_4$, 310.1050; found, 310.1045.

4-Methoxycarbonyl-5,6,7,8-tetrahydrobenzo[*f*]indole (39). A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **31** (0.080 g, 0.24 mmol) and 1.8 mL of CH_2Cl_2. Trifluoroacetic acid (0.55 mL, 0.81 g, 7.1 mmol) was added via syringe in one portion, and the resulting light brown solution was stirred at rt for 2 h. The reaction mixture was then diluted with 25 mL of Et_2O and extracted with 25 mL of satd $NaHCO_3$ solution. The aqueous layer was extracted with two 15-mL portions of Et_2O, and the combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.059 g of a pale orange oil. Column chromatography on 40 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 0.054 g (97%) of indoline **38** as a beige solid: mp 48-50 °C; IR (film) 3377, 2929, 2855, 1720, 1611, and 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.47 (s, 1H), 3.88 (s, 3H), 3.51 (t,

J = 8.3 Hz, 2H), 3.09 (t, J = 8.3 Hz, 2H), 2.78 (m, 2H), 2.70 (m, 2H), and 1.74 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 149.6, 137.1, 128.7, 127.7, 126.0, 112.4, 51.7, 47.4, 30.5, 30.3, 27.2, 23.6, and 23.0; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}NO_2$, 232.1332; found, 232.1340.

A threaded Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with indoline **38** (0.053 g, 0.23 mmol) and 3.2 mL of benzene. *o*-Chloranil (0.057 g, 0.23 mmol) was added in one portion and the resulting dark purple solution was stirred at rt for 15 min. The reaction mixture was then diluted with 25 mL of Et_2O and washed with two 20-mL portions of half-saturated Na_2CO_3 solution. The combined aqueous layers were extracted with two 20-mL portions of Et_2O, and the combined organic layers were washed with 25 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.067 g of a dark green solid. Column chromatography on 40 g of silica gel (gradient elution with 10-30% EtOAc-hexanes) provided 0.046 g (88%) of indole **39** as a white solid: mp 90-92 °C; IR (film) 3409, 2930, 2856, 1696, 1620, and 1434 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.18 (s, 1H), 7.15 (app s, 1H), 6.70 (app s, 1H), 4.01 (s, 3H), 3.12 (m, 2H), 2.93 (m, 2H), and 1.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 134.9, 132.3, 130.7, 125.9, 125.3, 121.9, 114.5, 102.7, 51.8, 30.9, 27.9, 23.7, and 23.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{15}NO_2$, 252.0995; found, 252.0992.

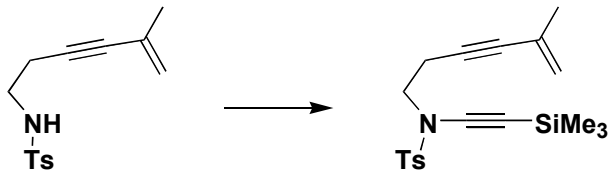
Part III. Experimental Procedures for the Preparation of Cycloaddition Substrates



40 **41**

***N*-(5-Methyl-5-hexen-3-ynyl)-*p*-toluenesulfonamide (41).** A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with $(Ph_3P)_2PdCl_2$ (0.377 g, 0.537 mmol), CuI (0.204 g, 1.07 mmol), alkyne **40** (2.000 g, 8.957 mmol), and 15 mL of THF. 2-Bromopropene (2.4 mL, 3.3 g, 27 mmol) and piperidine

(3.1 mL, 2.7 g, 31 mmol) were added sequentially via syringe, and the reaction mixture was heated at reflux for 90 min. The resulting suspension was allowed to cool to room temperature, diluted with 50 mL of Et_2O, and filtered through a 5 x 2.5 cm plug of silica gel with the aid of 300 mL of Et_2O. Concentration of the filtrate afforded 6.521 g of a brown oil. Column chromatography on 150 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 1.843 g (78%) of enyne **41** as a beige solid: mp 51-52 °C; IR ($CHCl_3$) 3384, 2953, 2258, 1613, 1599, 1410, 1334, and 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.21 (s, 1H), 5.18 (s, 1H), 4.85 (t, J = 6.4 Hz, 1H), 3.11 (dt, J = 6.4, 6.7 Hz, 2H), 2.46 (t, J = 6.7 Hz, 2H), 2.43 (s, 3H), and 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 137.1, 130.0, 127.3, 126.7, 122.0, 84.7, 84.3, 42.0, 23.8, 21.7, and 20.7; GC-MS *m/z*: 263 (M^+).

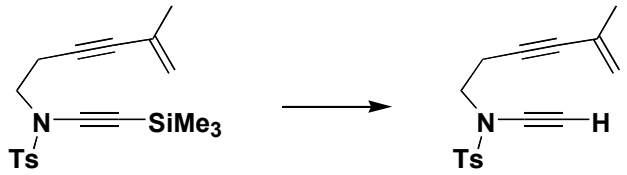


41 **6**

***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-[2-(trimethylsilyl)ethynyl]-*p*-toluenesulfonamide (6).** A 50-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with sulfonamide **41** (0.820 g, 3.11 mmol) and 30 mL of toluene. A solution of KHMDS (6.2 mL, 0.55 M in toluene, 3.4 mmol) was added via syringe over 5 min, and the resulting solution was stirred at rt for 1 h. A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with [2-(trimethylsilyl)ethynyl](phenyl)iodonium triflate[2] (1.680 g, 3.731 mmol) and 50 mL of toluene. The potassium sulfonamide solution was then added via cannula over 10 min (5-mL toluene rinse), and the resulting suspension was stirred at rt for 22 h. The reaction mixture was filtered through a 5 x 2.5 cm plug of silica gel with the aid of 500 mL of 20% EtOAc-hexanes, and then the filtrate was concentrated to provide 1.242 g of a brown oil. Column chromatography on 80 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.868 g (78%) of ynamide **6** as a pale yellow oil: IR ($CHCl_3$) 2959, 2254, 2158, 1612, 1597, 1371, and 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J =

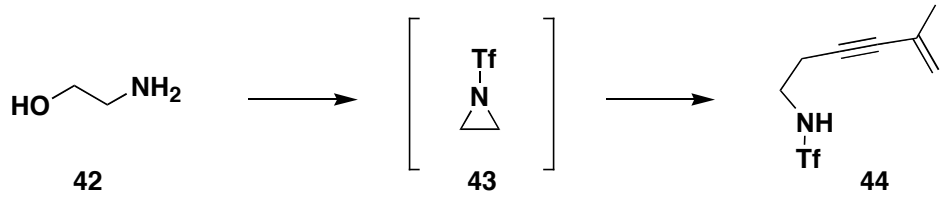
[2] Prepared according to the procedure of Bachi, M. D.; Bar-Ner, N.; Crittell, C. M.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1991**, *56*, 3912.

8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 5.21 (s, 1H), 5.17 (s, 1H), 3.50 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 2.46 (s, 3H), 1.84 (s, 3H), and 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 134.6, 129.9, 127.9, 126.9, 121.7, 94.5, 84.4, 83.9, 73.8, 50.3, 23.7, 21.9, 19.3, and 0.3; GC-MS *m/z*: 359 (M^+).



6 **7**

***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-(ethynyl)-*p*-toluenesulfonamide (7).** A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **6** (0.235 g, 0.654 mmol) and 20 mL of THF. The solution was cooled at 0 °C while 0.85 mL of *n*-Bu_4NF solution (1.0 M in THF, 0.85 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 20 min. The reaction mixture was diluted with 20 mL of Et_2O, washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.356 g of a dark red oil. Column chromatography on 30 g silica gel (elution with 5% EtOAc-hexanes) provided 0.156 g (83%) of ynamide **7** as a pale yellow oil: IR (neat) 3293, 2922, 2230, 2139, 1613, 1596, 1450, 1369, and 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.20 (s, 1H), 5.16 (s, 1H), 3.50 (t, J = 7.7 Hz, 2H), 2.79 (s, 1H), 2.65 (t, J = 7.7 Hz, 2H), 2.45 (s, 3H), and 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 134.5, 129.9, 127.6, 126.6, 121.5, 84.1, 83.8, 75.5, 59.7, 50.0, 23.5, 21.6, and 19.1; GC-MS *m/z*: 287 (M^+).



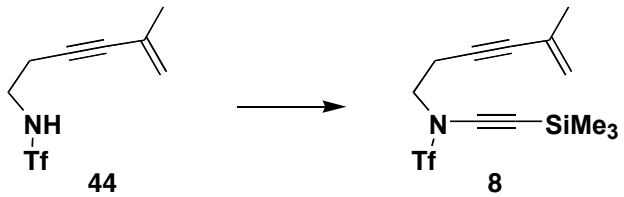
42 **43** **44**

***N*-(5-Methyl-5-hexen-3-ynyl)trifluoromethanesulfonamide (44).**[3] A 500-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 2-aminoethanol (**42**) (1.66

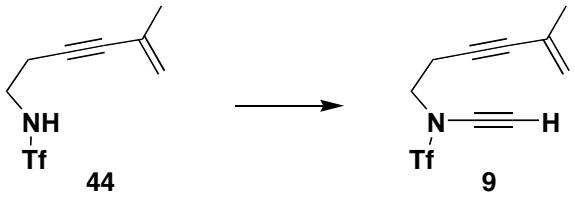
[3] This procedure is based on a method for the preparation of substituted aziridines described by Cernerud, M.; Skrinning, A.; Bérgère, I.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 3437.

mL, 1.68 g, 27.5 mmol), 180 mL of CH_2Cl_2, and triethylamine (7.7 mL, 5.6 g, 55 mmol). The solution was cooled at -78 °C while triflic anhydride (10.0 mL, 16.8 g, 59.4 mmol) was added dropwise via syringe over 40 min. The resulting mixture was stirred at -78 °C for 2 h, allowed to warm to -25 °C, and then stirred at -25 °C for 15 h. The solution was diluted with 150 mL of CH_2Cl_2, washed with two 150-mL portions of ice-cold 0.1 N HCl and two 150-mL portions of ice-cold satd $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and then diluted with 20 mL of THF. The resulting solution of aziridine **43** was concentrated to a volume of ca. 20 mL, diluted with another 20 mL portion of THF, and again concentrated to a volume of ca. 20 mL. This process was repeated two more times to remove CH_2Cl_2. The final solution of aziridine **43** in 40 mL of THF was dried over 3Å sieves for 1 h before use in the next step.

A 300-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 2-methyl-1-buten-3-yne (3.1 mL, 2.2 g, 33 mmol) and 70 mL of THF. The solution was cooled at -30 °C while 14.0 mL of *n*-BuLi solution (2.21 M in hexanes, 30.9 mmol) was added via syringe over 10 min. The resulting solution was stirred at -30 °C for 15 min and then the solution of aziridine **43** was added via cannula over 7 min (5-mL THF rinse). The resulting mixture was stirred at -30 °C for 20 h and then allowed to warm to room temperature. The reaction mixture was diluted with 50 mL of satd NH_4Cl solution and 200 mL of CH_2Cl_2, and washed with 150 mL of 0.1 N HCl. The aqueous phase was extracted with three 100-mL portions of CH_2Cl_2, and the combined organic layers were washed with 150 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 9.185 g of a dark red oil. Column chromatography on 250 g of silica gel (elution with 5% EtOAc-hexanes) provided 3.396 g (51% overall from **42**) of triflamide **44** as an orange oil: IR ($CHCl_3$) 3379, 2957, 2254, 1614, 1429, 1378, and 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (br s, 1H), 5.27 (s, 1H), 5.23 (s, 1H), 3.44 (app q, J = 6.4 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), and 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.4, 122.2, 119.6 (q, J_{CF} = 530 Hz), 84.9, 83.5, 43.3, 23.7, and 21.6; GC-MS *m/z*: 241 (M^+).

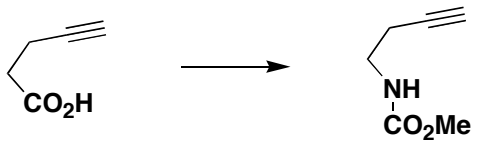


***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-[2-(trimethylsilyl)ethynyl]trifluoromethanesulfonamide (8).** A 50-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflamide **44** (0.560 g, 2.32 mmol), 15 mL of toluene, and 5 mL of THF. A solution of KHMDS (4.6 mL, 0.55 M in toluene, 2.5 mmol) was added via syringe over 3 min, and the resulting solution was stirred at rt for 10 min. A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with [2-(trimethylsilyl)ethynyl](phenyl)iodonium triflate[2] (1.250 g, 2.776 mmol) and 25 mL of toluene. The potassium triflamide solution was then added via cannula over 5 min, and the resulting suspension was stirred at rt for 24 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with 50 mL of satd NaCl solution. The aqueous layer was extracted with two 50-mL portions of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide 1.252 g of a red oil. Column chromatography on 30 g of silica gel (gradient elution with 0-2% EtOAc-hexanes) provided 0.545 g (70%) of ynamide **8** as a pale yellow oil: IR ($CHCl_3$) 2961, 2254, 2186, 1614, 1414, and 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1H), 5.21 (s, 1H), 3.71 (t, J = 7.3 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 1.87 (s, 3H), and 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.7, 122.1, 119.9 (q, J_{CF} = 322 Hz), 89.7, 84.7, 82.9, 74.9, 52.2, 23.6, 19.4, and -0.1; GC-MS *m/z*: 337 (M^+).



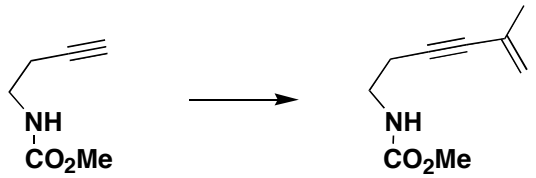
***N*-(5-Methyl-5-hexen-3-ynyl)-*N*-(ethynyl)trifluoromethanesulfonamide (9).** A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, two rubber septa, and an argon inlet needle was charged with triflamide **44** (0.460 g, 1.91 mmol), 19 mL of DMF, and Cs_2CO_3 (0.690 g, 2.12 mmol). A solution of [2-(trimethylsilyl)ethynyl](phenyl)iodonium triflate[2] (1.040 g, 2.310 mmol) in 25 mL of CH_2Cl_2 was added via cannula in one portion (5-mL CH_2Cl_2 rinse), and the resulting solution was allowed to stir at rt for 16 h. The reaction mixture was then diluted with 200 mL of Et_2O and washed with four 200-mL portions of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.909 g of a pale brown oil. Column chromatography on 50 g of silica gel (elution with 2% EtOAc-hexanes) provided

0.437 g (87%) of ynamide **9** as a pale yellow oil: IR ($CHCl_3$) 3318, 2957, 2263, 2154, 1614, 1420, 1349, and 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26 (s, 1H), 5.21 (s, 1H), 3.74 (t, J = 7.2 Hz, 2H), 2.83 (s, 1H), 2.79 (t, J = 7.2 Hz, 2H), and 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.6, 122.0, 119.7 (q, J_{CF} = 322 Hz), 84.8, 82.7, 71.5, 60.3, 52.1, 23.5, and 19.4; GC-MS *m/z*: 265 (M^+).



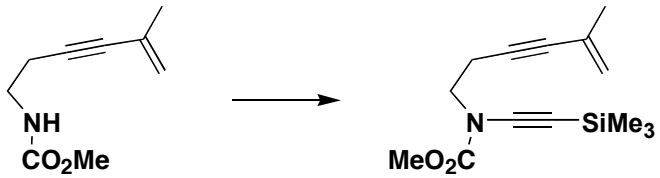
45 **4**

***N*-(Methoxycarbonyl)-3-butynylamine (4).** A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with 4-pentynoic acid (**45**) (5.174 g, 52.74 mmol), 75 mL of toluene, and triethylamine (7.4 mL, 5.4 g, 53 mmol). Diphenylphosphoryl azide (11.4 mL, 14.6 g, 52.9 mmol) was added via syringe over 5 min, and the resulting solution was heated at 80 °C (bath temperature) until bubbling ceased (2 h). The oil bath was cooled to 50 °C, methanol (22 mL, 17 g, 540 mmol) was added and the resulting mixture was stirred at 50 °C for 14 h. The reaction mixture was allowed to cool to room temperature and the toluene and methanol were removed by rotary evaporation at rt and 20 mmHg. The resulting yellow oil was diluted with 100 mL of Et_2O, 50 mL of water, and 10 mL of satd Na_2CO_3 solution. The aqueous layer was separated and extracted with ten 50-mL portions of Et_2O, and the combined organic layers were washed with 200 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 7.102 g of a yellow oil. Column chromatography on 140 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 5.861 g (87%) of carbamate **4** as a pale yellow oil: IR (CH_2Cl_2) 3446, 3304, 2954, 2121, 1721, 1520, and 1469 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 and 5.17 (NH rotamers, br s, 1H), 3.64 (s, 3H), 3.31 (app q, J = 6.4 Hz, 2H), 2.37 (dt, J = 2.4, 6.4 Hz, 2H), and 1.99 (t, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 81.5, 70.0, 52.2, 39.7, and 19.9; GC-MS *m/z*: 127 (M^+).



4 46

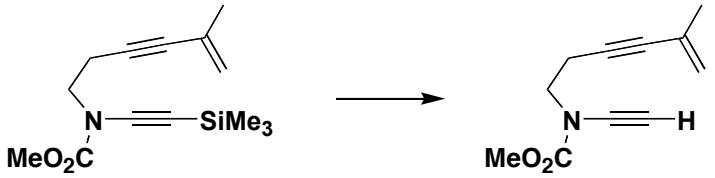
***N*-(Methoxycarbonyl)-5-methyl-5-hexen-3-ynylamine (46).** A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with $(Ph_3P)_2PdCl_2$ (0.445 g, 0.634 mmol), CuI (0.234 g, 1.28 mmol), alkyne **4** (2.685 g, 21.12 mmol), and 35 mL of THF. 2-Bromopropene (2.8 mL, 3.8 g, 32 mmol) and piperidine (7.3 mL, 6.3 g, 74 mmol) were added sequentially via syringe, and the reaction mixture was heated at reflux for 5 h. The resulting suspension was allowed to cool to room temperature, diluted with 300 mL of Et_2O, and filtered through a 5 x 2.5 cm plug of silica gel with the aid of 400 mL of Et_2O. Concentration of the filtrate afforded 4.426 g of a brown oil. Column chromatography on 100 g of silica gel (elution with 10% EtOAc-hexanes) provided 2.972 g (84%) of enyne **46** as a pale brown oil: IR (neat) 3336, 2951, 2228, 1704, 1614, 1536, and 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.16 (s, 1H), 4.90 and 5.06 (NH rotamers, br s, 1H), 3.66 (s, 3H), 3.32 (dt, J = 5.3, 5.8 Hz, 2H), 2.50 (t, J = 5.8 Hz, 2H), and 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 127.0, 121.4, 86.0, 83.5, 52.3, 40.1, 23.8, and 20.9; GC-MS *m/z*: 167 (M^+).



46 5

General Procedure for the N-Alkynylation of Carbamates with Bromo Alkynes. *N*-(Methoxycarbonyl)-*N*-[2-(trimethylsilyl)ethynyl]-5-methyl-5-hexen-3-ynylamine (5). A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and addition funnel fitted with rubber septum and argon inlet needle was charged with carbamate **46** (0.700 g, 4.19 mmol) and 17 mL of pyridine. The solution was cooled at 0 °C while 4.6 mL of KHMDS solution (0.91 M in THF,

4.2 mmol) was added via syringe over 3 min, and the resulting viscous mixture was stirred at 0 °C for 10 min. A solution of CuI (0.799 g, 4.20 mmol) in 9 mL of pyridine was added via cannula in one portion (1-mL pyridine rinse). The ice bath was removed, and the resulting solution was stirred at rt for 2 h. A solution of 1-bromo-2-(trimethylsilyl)ethyne[4] (14 mL, 0.60 M in benzene, 8.4 mmol) was then added via the addition funnel over 1 h, and the resulting mixture was stirred at rt for 20 h. The reaction mixture was diluted with 250 mL of Et_2O and washed with three 100-mL portions of a 2:1 mixture of satd NaCl solution and conc NH_4OH solution. The combined aqueous layers were extracted with four 150-mL portions of Et_2O, and the combined organic layers were washed with 200 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.458 g of a dark brown oil. Column chromatography on 80 g of silica gel (gradient elution with 0-3% EtOAc-hexanes) provided 0.646 g (59%) of ynamide **5** as a yellow oil: IR (neat) 2957, 2231, 2178, 1736, 1614, and 1441 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 5.13 (s, 1H), 3.77 (s, 3H), 3.60 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.82 (s, 3H), and 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 126.9, 121.3, 95.0, 84.8, 83.5, 72.6, 54.2, 49.0, 23.7, 18.6, and 0.3; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{21}NO_2Si$, 286.1234; found, 286.1245.

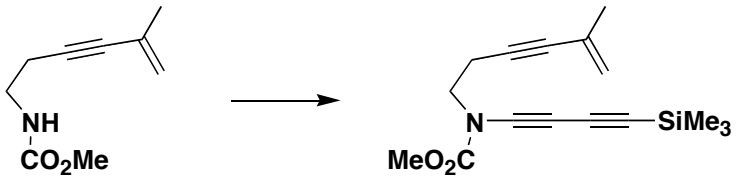


5 **10**

***N*-(Methoxycarbonyl)-*N*-(ethynyl)-5-methyl-5-hexen-3-ynylamine (10).** A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **5** (0.489 g, 1.85 mmol) and 60 mL of THF. The solution was cooled at 0 °C while 2.4 mL of *n*-Bu_4NF solution (1.0 M in THF, 2.4 mmol) was added via syringe, and the resulting dark red solution was stirred at 0 °C for 20 min. The reaction mixture was diluted with 80 mL of Et_2O, washed with 80 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.566 g of a dark red oil. Column chromatography on 80 g silica gel (elution with 3% EtOAc-hexanes) provided 0.272 g (77%) of ynamide **10** as a pale yellow oil: IR (neat) 3297, 2956, 2230, 2146, 1733, 1614, and 1442 cm^{-1}; ^1H NMR (500

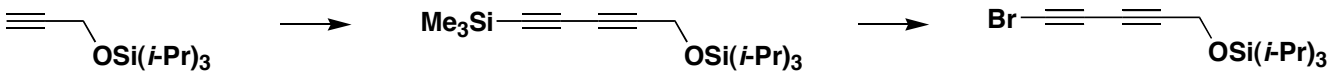
[4] Prepared according to the procedure of Miller, J. A.; Zweifel, G. *Synthesis* **1983**, 128.

MHz, $CDCl_3$) δ 5.17 (s, 1H), 5.11 (s, 1H), 3.77 (s, 3H), 3.60 (t, J = 7.3 Hz, 2H), 2.82 (s, 1H), 2.62 (t, J = 7.3 Hz, 2H), and 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 126.8, 121.3, 84.6, 83.6, 76.0, 59.1, 54.2, 48.7, 23.5, and 18.6; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{13}NO_2$, 214.0838; found, 214.0837.



46 **11**

***N*-(Methoxycarbonyl)-*N*-[4-(trimethylsilyl)-1,3-butadiynyl]-5-methyl-5-hexen-3-ynylamine (11).** Reaction of a solution of carbamate **46** (0.287 g, 1.72 mmol) in 7.0 mL of pyridine with KHMDS (1.9 mL, 0.91 M in THF, 1.7 mmol), CuI (0.330 g, 1.73 mmol) in 3.6 mL of pyridine, and 1-bromo-4-(trimethylsilyl)-1,3-butadiyne[5] (8.5 mL, 0.40 M in benzene, 3.4 mmol) according to the general procedure gave 0.659 g of a dark brown oil. Column chromatography on 50 g of silica gel (elution with benzene) provided 0.147 g (30%) of ynamide **11** as a yellow oil: IR (neat) 2957, 2233, 2113, 1743, 1613, and 1440 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.15 (s, 1H), 3.80 (s, 3H), 3.63 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 7.2 Hz, 2H), 1.83 (s, 3H), and 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 126.8, 121.5, 90.0, 87.5, 84.3, 83.9, 69.2, 58.5, 54.5, 49.0, 23.6, 18.9, and –0.3; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{21}NO_2Si$, 310.1234; found, 310.1231.



47 **48** **49**

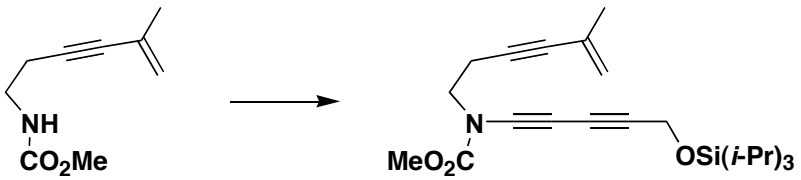
1-Bromo-5-(triisopropylsiloxy)-1,3-pentadiyne (49). A 200-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet needle, and a short path distillation head fitted with a 100-mL, collection flask was charged with alkyne **47** (3.177 g, 14.96 mmol) and 24 mL of THF. The solution was cooled at -78 °C while 6.24 mL of *n*-BuLi solution (2.40 M in hexanes, 15.0 mmol) was

[5] Prepared according to the procedure of Basak, S.; Srivastava, S.; le Noble, W. J. *J. Org. Chem.* **1987**, *52*, 5095.

added via syringe over 10 min, and the pale yellow solution was allowed to stir at -78 °C for 20 min. The dry ice-acetone bath was replaced with an ice bath and the solution was stirred at 0 °C while CuI (2.848 g, 14.95 mmol) was added in one portion. The ice bath was removed and the yellow, viscous mixture was stirred at rt for 30 min. Next, THF and hexane were removed by distillation (rt, 0.5 mmHg) while cooling the collection flask at -78 °C. The remaining copper acetylide was dried at 0.5 mmHg for 30 min, and then the system was vented to argon and 48 mL of pyridine was added. 1-Iodo-2-(trimethylsilyl)ethyne[6] (2.95 g, 15.0 mmol) was added via cannula in one portion (2-mL pyridine rinse), and the resulting viscous suspension was stirred at rt for 1 h. The reaction mixture was diluted with 300 mL of hexane and washed with three 200-mL portions of conc NH_4OH solution. The combined aqueous layers were diluted with 250 mL of satd NaCl solution, extracted with four 200-mL portions of hexane, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 3.735 g of a dark brown oil. Two successive purifications by column chromatography on 120 g of silica gel (gradient elution with 0-0.5% EtOAc-hexanes) provided 1.623 g (35%) of diyne **48** as a deep yellow oil.

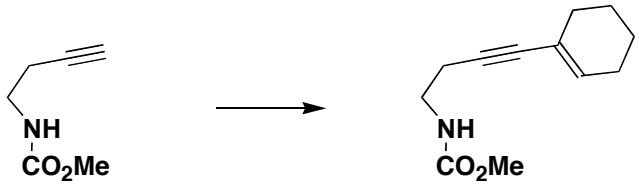
A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diyne **48** (1.616 g, 5.236 mmol), NBS (1.027 g, 5.770 mmol), and 35 mL of acetone. Silver(I) nitrate (0.136 g, 0.801 mmol) was added in one portion, the flask was wrapped with aluminum foil, and the resulting suspension was stirred at rt for 15 h. The reaction mixture was diluted with 100 mL of pentane, washed with three 100-mL portions of satd $Na_2S_2O_3$ solution and 100 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.224 g (74%) of bromo diyne **49** as an orange oil contaminated with 4% of unreacted **48**. This material was dissolved in 6.1 mL of benzene and stored at –20 °C as a 0.60 M stock solution. Data for **49**: IR (neat) 2944, 2867, 2239, 2108, and 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43 (s, 2H), 1.10 (sept, J = 6.3 Hz, 3H), and 1.09 (d, J = 6.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.1, 69.8, 67.9, 65.2, 52.4, 18.1, and 12.2; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{23}BrOSi$, 337.0594; found, 337.0607.

[6] Prepared according to the procedure of Siegel, K.; Brückner, R. *Synlett* **1999**, *8*, 1227.



46 **12**

***N*-(Methoxycarbonyl)-*N*-[5-(triisopropylsiloxy)-1,3-pentadiynyl]-5-methyl-5-hexen-3-ynylamine (12).** Reaction of a solution of carbamate **46** (0.414 g, 2.48 mmol) in 10 mL of pyridine with KHMDS (2.8 mL, 0.90 M in THF, 2.5 mmol), CuI (0.480 g, 2.52 mmol) in 5 mL of pyridine, and bromo diyne **49** (6.1 mL, 0.60 M in benzene, 3.7 mmol) according to the general procedure gave 1.499 g of a dark brown oil. Column chromatography on 100 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.494 g (50%) of ynamide **12** as a red oil: IR (neat) 2945, 2866, 2259, 2172, 1741, 1613, and 1441 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 1H), 5.18 (s, 1H), 4.49 (s, 2H), 3.83 (s, 3H), 3.66 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.86 (s, 3H), 1.13 (sept, J = 5.5 Hz, 3H), and 1.08 (d, J = 5.5 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 126.8, 121.4, 84.4, 83.9, 81.3, 70.5, 68.8, 57.7, 54.5, 52.6, 49.1, 23.6, 18.9, 18.0, and 12.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{35}NO_3Si$, 424.2278; found, 424.2269.

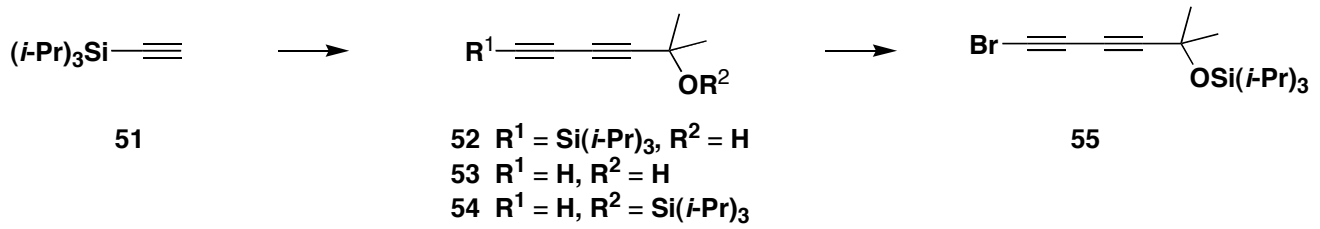


4 **50**

***N*-(Methoxycarbonyl)-4-(1-cyclohexenyl)-3-butynylamine (50).** A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with $(Ph_3P)_2PdCl_2$ (0.233 g, 0.332 mmol), CuI (0.122 g, 0.641 mmol), and alkyne **4** (0.695 g, 5.47 mmol). A solution of 1-(trifluoromethanesulfonyl)cyclohexene[7] (8.6 mL, 1.0 M in THF, 8.6 mmol) was added, followed by piperidine (1.9 mL, 1.6 g, 19 mmol), and the resulting suspension was stirred at room temperature for 2 h. The reaction mixture was diluted with 100 mL of Et_2O and then filtered through a 5

[7] Prepared according to the procedure of Stang, P. J.; Treptow, W. *Synthesis* **1980**, *4*, 283.

x 2.5 cm plug of silica gel with the aid of 300 mL of Et_2O. Concentration of the filtrate afforded 2.051 g of a brown oil. Column chromatography on 120 g of silica gel (gradient elution with 0-10% EtOAc-hexanes) provided 0.852 g (75%) of enyne **50** as a yellow oil: IR (neat) 3336, 2932, 2223, 1707, 1536, and 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 4.85 and 5.01 (NH rotamers, br s, 1H), 3.66 (s, 3H), 3.31 (app q, J = 6.1 Hz, 2H), 2.49 (t, J = 6.1 Hz, 2H), 2.04-2.09 (m, 4H), and 1.53-1.63 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 134.3, 120.7, 84.1, 83.9, 52.3, 40.2, 29.6, 25.7, 22.5, 21.7, and 20.9; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{17}NO_2$, 230.1151; found, 230.1153.



51 **52** R^1 = Si(*i*-Pr)$_3$, R^2 = H; **53** R^1 = H, R^2 = H; **54** R^1 = H, R^2 = Si(*i*-Pr)$_3$ **55**

1-Bromo-5-(triisopropylsiloxy)-5-methyl-1,3-hexadiyne (55). A 100-mL, three-necked, round-bottomed flask equipped with two glass stoppers and an argon inlet adapter was charged with CuCl (0.097 g, 0.98 mmol) and 40 mL of aqueous butylamine (30% wt in H_2O) solution. A few crystals of NH_2OH•HCl were added until the blue solution became colorless (ca. 0.010 g). Triisopropylsilyl acetylene (**51**) (13 mL, 11 g, 58 mmol) was added in one portion, and the mixture was cooled at 0 °C while 1-bromo-3-hydroxy-3-methylbutyne[8] (7.8 g, 48 mmol) was added via cannula over 5 min. The ice bath was removed and the reaction mixture was allowed to stir at rt for 30 min while crystals of NH_2OH•HCl were added (ca. 0.010 g portions) as necessary to prevent the mixture from turning blue or green. The resulting beige mixture was extracted with six 50-mL portions of Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 13.653 g of a white solid. Column chromatography on 150 g of silica gel (gradient elution with 0-50% EtOAc-hexanes) provided 5.743 g (45%) of diyne **52** as a white solid: mp 53-55 °C; IR (film) 3339, 2944, 2866, 2230, 2101, and 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.06 (br s, 1H), 1.55 (s, 6H), and 1.09 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.0, 85.1, 80.8, 67.9, 65.8, 31.3, 18.7, and 11.4; GC-MS *m/z*: 264 (M^+).

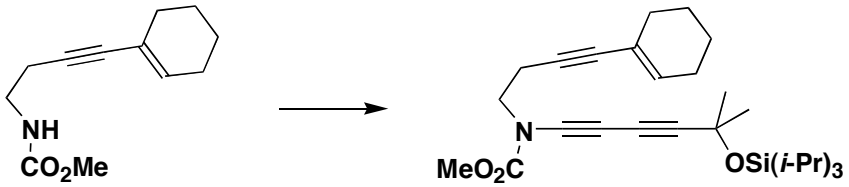
[8] Prepared according to the procedure of Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841.

A 250-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diyne **52** (5.703 g, 21.56 mmol) and 150 mL of THF. The solution was cooled at 0 °C while 28 mL of *n*-Bu_4NF solution (1.0 M in THF, 28 mmol) was added via syringe, and the resulting yellow solution was stirred at 0 °C for 10 min. The reaction mixture was diluted with 150 mL of Et_2O, 150 mL of water, and 50 mL of satd NaCl solution. The aqueous layer was separated and extracted with two 150-mL portions of Et_2O, and the combined organic layers were washed with 300 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 5.556 g of a dark red oil. Column chromatography on 80 g silica gel (gradient elution with 3-5% EtOAc-hexanes) provided 1.952 g (84%, 90% pure by ^1H NMR analysis) of the desired desilylated diyne **53** as an orange oil contaminated with triisopropylsilanol.

A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with diyne **53** (1.906 g, 90% purity, ca. 15 mmol) and 100 mL of CH_2Cl_2. The solution was cooled at 0 °C while 2,6-lutidine (2.6 mL, 2.4 g, 22 mmol) and triispropylsilyl triflate (4.8 mL, 5.5 g, 18 mmol) were added sequentially via syringe. The ice bath was then removed and the reaction mixture was heated at reflux for 36 h and then allowed to cool to room temperature. The solution was washed with two 50-mL portions of 5% HCl, 50 mL of water, 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 4.386 g of an orange oil. Column chromatography on 100 g silica gel (elution with pentanes) provided 3.250 g (57% overall from **52**) of diyne **54** as a colorless oil: IR (neat) 3314, 2944, 2867, 2230, 2063, and 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 1H), 1.54 (s, 6H), 1.15 (sept, J = 6.4 Hz, 3H), and 1.09 (d, J = 6.4 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.8, 68.4, 67.9, 67.2, 66.6, 33.0, 18.5, and 13.1; GC-MS *m/z*: 264 (M^+).

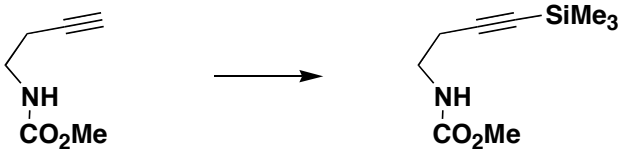
A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diyne **54** (3.201 g, 12.10 mmol), NBS (3.225 g, 18.12 mmol), and 40 mL of acetone. Silver(I) nitrate (0.215 g, 1.27 mmol) was added in one portion, the flask was wrapped with aluminum foil, and the resulting suspension was stirred at rt for 20 h. The reaction mixture was then diluted with 200 mL of hexanes, washed with five 50-mL portions of satd $Na_2S_2O_3$ solution, and the combined aqueous layers were back-extracted with three 50-mL portions of hexane. The combined organic layers were washed with 200 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.075 g (98%) of bromo diyne **55** as an orange oil which was dissolved in 20 mL of benzene and stored at

–20 °C as a 0.58 M stock solution. Data for **55**: IR (neat) 2962, 2867, 2248, 2136, and 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 6H), 1.14 (sept, J = 6.4 Hz, 3H), and 1.08 (d, J = 6.4 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.5, 67.9, 66.6, 65.1, 41.3, 33.1, 18.5, and 13.1. HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{27}BrOSi$, 365.0907; found, 365.0894.



50 **13**

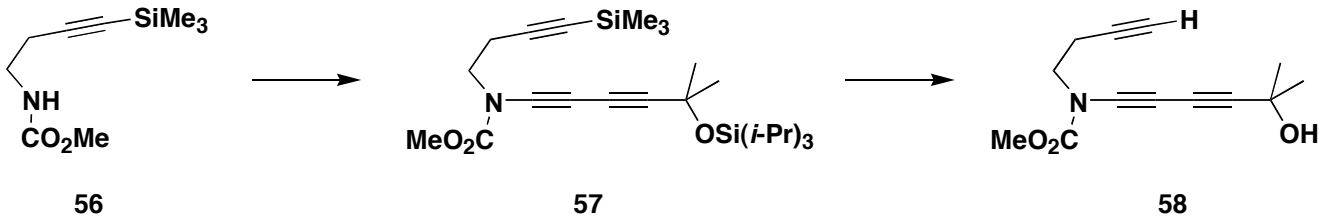
***N*-(Methoxycarbonyl)-*N*-[4-(1-Cyclohexenyl)-3-butnynl]-5-(triisopropylsiloxy)-5-methyl-1,3-hexadiynylamine (13).** Reaction of a solution of carbamate **50** (0.212 g, 1.02 mmol) in 4.0 mL of pyridine with KHMDS (1.13 mL, 0.90 M in THF, 1.0 mmol), CuI (0.195 g, 1.03 mmol) in 2.0 mL of pyridine, and bromo diyne **55** (2.6 mL, 0.58 M in benzene, 1.5 mmol) according to the general procedure gave 0.596 g of a dark brown oil. Column chromatography on 40 g of silica gel (gradient elution with 0-15% EtOAc-hexanes) provided 0.244 g (51%) of ynamide **13** as a pale brown oil: IR (neat) 2942, 2865, 2253, 2167, 1738, and 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (m, 1H), 3.79 (s, 3H), 3.61 (t, J = 7.3 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.01-2.06 (m, 4H), 1.52-1.60 (m, 4H), 1.50 (s, 6H), 1.11 (sept, J = 6.7 Hz, 3H), and 1.04 (d, J = 6.7 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 134.3, 120.7, 87.6, 84.4, 82.4, 70.9, 67.0, 66.8, 57.4, 54.5, 49.3, 33.1, 29.4, 25.7, 22.5, 21.7, 18.9, 18.4, and 13.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{43}NO_3Si$, 492.2904; found, 492.2906.



4 **56**

***N*-(Methoxycarbonyl)-4-(trimethylsilyl)-3-butynylamine (56).** A 250-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **4** (3.346 g, 26.32

mmol) and 130 mL of THF and cooled at -78 °C while 22.4 mL of *n*-BuLi solution (2.35 M in hexanes, 52.6 mmol) was added via syringe over 5 min. The resulting viscous, white mixture was stirred at -78 °C for 15 min. Chlorotrimethylsilane (6.7 mL, 5.7 g, 53 mmol) was then added via syringe over 2 min, the ice bath was removed, and the resulting solution was stirred at rt for 90 min. 2 M HCl (60 mL) was next added, and the biphasic solution was stirred at rt for 1 h. The volatile organic solvents (THF and hexanes) were removed by rotary evaporation at rt and 20 mmHg, and the resulting aqueous solution was extracted with three 100-mL portions of Et_2O. The combined organic layers were washed with 150 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 5.376 g of a yellow oil. Column chromatography on 120 g silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 4.420 g (84%) of silyl alkyne **56** as a colorless oil: IR (neat) 3338, 2958, 2177, 1708, 1535, and 1449 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 and 5.06 (NH rotamers, br s, 1H), 3.65 (s, 3H), 3.30 (dt, J = 6.1, 6.4 Hz, 2H), 2.41 (t, J = 6.4 Hz, 2H), and 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 103.9, 86.1, 51.9, 39.7, 21.1, and -0.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_9H_{17}NO_2Si$, 222.0921; found, 222.0920.

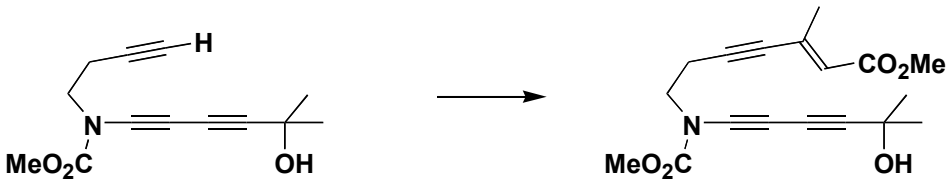


56 **57** **58**

***N*-(3-Butynyl)-*N*-(methoxycarbonyl)-5-hydroxy-5-methyl-1,3-hexadiynylamine (58).** Reaction of a solution of carbamate **56** (0.768 g, 3.85 mmol) in 15 mL of pyridine with KHMDS (4.3 mL, 0.91 M in THF, 3.9 mmol), CuI (0.744 g, 3.91 mmol) in 8 mL of pyridine, and bromo diyne **55** (8.4 mL, 0.60 M in benzene, 5.0 mmol) according to the general procedure gave 2.127 g of a dark red oil. Column chromatography on 80 g of silica gel (gradient elution with 0-2% EtOAc-hexanes) provided 1.104 g (62%, 87% pure by ^1H NMR analysis) of ynamide **57** as a dark red oil that was used in the next step without further purification.

A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **57** (1.104 g, 87% purity, ca. 2.1 mmol) and 50 mL of THF. The solution was cooled at 0 °C while 5.2 mL of *n*-Bu_4NF solution (1.0 M in THF, 5.2 mmol) was added via syringe over 2

min. The resulting dark purple solution was stirred at 0 °C for 15 min and then diluted with 100 mL of Et_2O and extracted with 50 mL of water. The aqueous layer was extracted with two 25-mL portions of Et_2O, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.968 g of a dark brown oil. Column chromatography on 40 g silica gel (gradient elution with 20-30% EtOAc-hexanes) provided 0.463 g (52% overall from **56**) of ynamide **58** as a yellow oil: IR (neat) 3452, 3296, 2982, 2255, 2167, 1738, and 1442 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.63 (t, J = 7.2 Hz, 2H), 2.59 (s, 1H), 2.53 (dt, J = 2.5, 7.2 Hz, 2H), 2.01 (t, J = 2.5 Hz, 1H), and 1.51 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 86.9, 79.8, 70.7, 70.7, 66.3, 65.7, 57.4, 54.7, 48.6, 31.2, and 17.9; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}NO_3$, 234.1125; found, 234.1129.

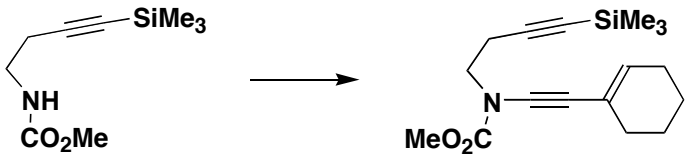


58 **14**

***N*-(Methoxycarbonyl)-*N*-(6-methoxycarbonyl-5-methyl-5-hexen-3-ynyl)-5-hydroxy-5-methyl-1,3-hexadiynylamine (14).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with $(Ph_3P)_2PdCl_2$ (0.041 g, 0.058 mmol) and CuI (0.023 g, 0.12 mmol) and cooled at 0 °C while a solution of alkyne **58** (0.459 g, 1.97 mmol) in 2.0 mL of Et_3N was added via cannula in one portion (two 0.5-mL Et_3N rinses). A solution of methyl (*E*)-3-iodo-2-butenoate[9] (3.0 mL, 1.0 M in THF, 3.0 mmol) was added, the ice bath was removed, and the resulting dark red suspension was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of Et_2O and filtered through a 5 x 2.5 cm plug of silica gel with the aid of 300 mL of Et_2O. Concentration of the filtrate afforded 0.720 g of a dark red oil. Column chromatography on 40 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.399 g (61%) of enyne **14** as a beige solid: mp 73-74 °C; IR (film) 3471, 2982, 2955, 2255, 2168, 1738, 1721, 1618, and 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.68 (t, J = 6.6 Hz, 2H), 2.72 (t, J = 6.6 Hz, 2H), 2.41 (br s, 1H), 2.27 (s, 3H),

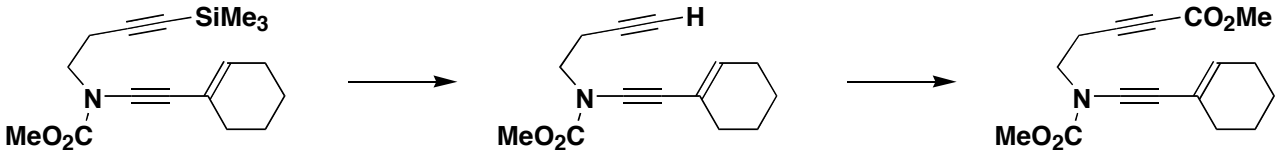
[9] Prepared according to the procedure of Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407.

and 1.53 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 155.4, 138.3, 123.5, 90.8, 87.1, 84.7, 70.7, 66.0, 65.3, 57.3, 54.5, 51.2, 48.6, 31.0, 19.9, and 19.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{21}NO_5$, 354.1312; found, 354.1316.



56 **59**

***N*-(Methoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-(trimethylsilyl)-3-butynylamine (59).** Reaction of a solution of carbamate **56** (0.617 g, 3.10 mmol) in 14 mL of pyridine with KHMDS (3.5 mL, 0.90 M in THF, 3.2 mmol), CuI (0.600 g, 3.15 mmol) in 6 mL of pyridine, and 1-bromo-2-(1-cyclohexenyl)ethyne[10] (10.5 mL, 0.59 M in benzene, 6.2 mmol) according to the general procedure gave 1.266 g of a dark red oil. Column chromatography on 140 g of silica gel (gradient elution with 0-1% EtOAc-hexanes) provided 0.572 g (61%) of ynamide **59** as a pale yellow oil: IR (neat) 2933, 2239, 2179, 1730, and 1441 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (m, 1H), 3.76 (s, 1H), 3.61 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 2.04-2.11 (m, 4H), 1.60 (m, 2H), 1.55 (m, 2H), and 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 133.8, 120.2, 102.8, 86.7, 79.9, 72.3, 54.1, 49.2, 29.7, 25.8, 22.5, 21.7, 19.3, and 0.1; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{17}H_{25}NO_2Si$, 304.1727; found, 304.1726.



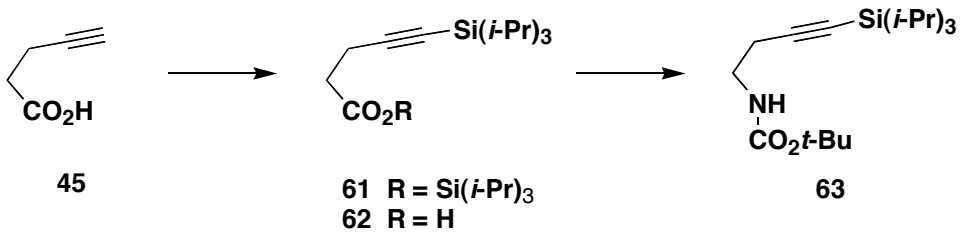
59 **60** **25**

***N*-(Methoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-methoxycarbonyl-3-butnynlamine (25).** A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with silyl alkyne **59** (0.572 g, 1.88 mmol) and 38 mL of THF. The solution was cooled at 0 °C while 2.1 mL of *n*-Bu_4NF solution (1.0 M in THF, 2.1 mmol) was added via syringe, and the resulting

[10] Prepared from 1-(cyclohexenyl)ethyne, NBS, and catalytic $AgNO_3$ according to the procedure of Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.

dark red solution was stirred at 0 °C for 10 min. The reaction mixture was diluted with 40 mL of Et_2O and extracted with 40 mL of water. The aqueous layer was extracted with two 25-mL portions of Et_2O, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.445 g of a dark red oil. Column chromatography on 30 g silica gel (elution with 5% EtOAc-hexanes) provided 0.387 g (89%) of desilylated alkyne **60** as a pale yellow oil: IR (neat) 3289, 2932, 2239, 2122, 1730, and 1441 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (m, 1H), 3.81 (s, 3H), 3.67 (t, J = 7.3 Hz, 2H), 2.57 (dt, J = 2.7, 7.3 Hz, 2H), 2.08-2.15 (m, 4H), 2.00 (t, J = 2.7 Hz, 1H), 1.64 (m, 2H), and 1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 133.9, 120.0, 80.3, 79.5, 72.3, 70.2, 54.1, 48.8, 29.6, 25.7, 22.4, 21.6, and 17.7; GC-MS *m/z*: 231 (M^+).

A 25-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **60** (0.364 g, 1.57 mmol) and 16 mL of THF. The solution was cooled at -78 °C while 2.0 mL of LiHMDS solution (1.03 M in THF, 2.1 mmol) was added via syringe over 1 min, and the resulting yellow solution was stirred at -78 °C for 2 h. Methyl chloroformate (1.2 mL, 1.5 g, 16 mmol) was then added in one portion via syringe, and the resulting mixture was stirred at -78 °C for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0 °C for 1 h and then diluted with 60 mL of Et_2O. The solution was extracted with 30 mL of a 2:1 mixture of conc NH_4OH solution and satd NaCl solution, and the aqueous layer was extracted with two 20-mL portions of Et_2O. The combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.835 g of a mixture of yellow oil and white needles. Column chromatography on 40 g silica gel (elution with 15% EtOAc-hexanes) provided 0.325 g (72%) of ynamide **25** as a colorless oil: IR (neat) 2932, 2241, 1722, 1692, and 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.70 (t, J = 7.3 Hz, 2H), 2.70 (t, J = 7.3 Hz, 2H), 2.09 (m, 4H), 1.62 (m, 2H), and 1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 154.0, 134.5, 119.9, 85.3, 79.3, 74.3, 72.7, 54.4, 52.8, 48.1, 29.6, 25.8, 22.5, 21.6, and 18.2; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}NO_4$, 290.1387; found, 290.1374.

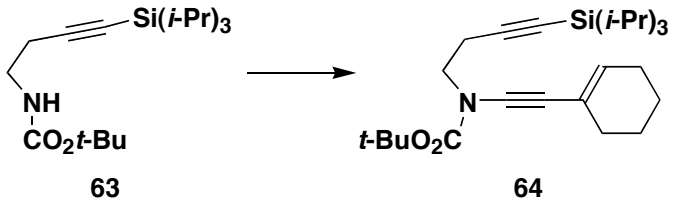


45 61 R = Si(*i*-Pr)$_3$ 62 R = H 63

***N*-(*tert*-Butoxycarbonyl)-4-(triisopropylsilyl)-3-butynylamine (63).** A 1-L, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 4-pentynoic acid (**45**) (3.522 g, 35.90 mmol) and 300 mL of THF and cooled at -78 °C while 30 mL of *n*-BuLi solution (2.45 M in hexanes, 74 mmol) was added via syringe over 3 min. The resulting white mixture was stirred at -78 °C for 30 min. Chlorotriisopropylsilane (17 mL, 15 g, 79 mmol) was added via syringe in one portion, the ice bath was removed, and the resulting solution was stirred at rt for 2 h. The reaction mixture was diluted with 100 mL of water and 200 mL of satd NaCl solution, and the aqueous layer was separated and extracted with two 100-mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 17.268 g of **61** as a yellow oil.

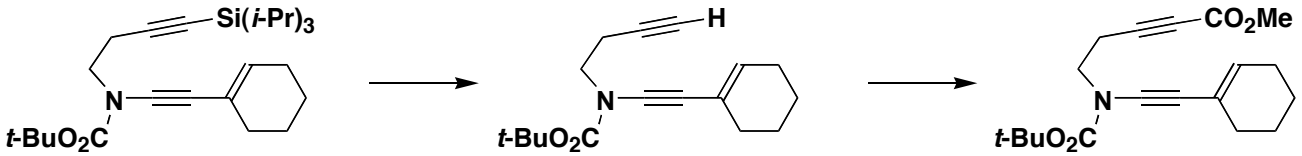
A 500-mL, round-bottomed flask equipped with an argon inlet adapter was charged with a solution of **61** in 160 mL of THF, 40 mL of methanol, and 40 mL of water. Potassium carbonate (24.8 g, 180 mmol) was added in one portion and the reaction mixture was vigorously stirred for 1 h. The resulting suspension was then diluted with 200 mL of CH_2Cl_2 and 100 mL of satd NaCl solution, and 2 M HCl was added dropwise to adjust the pH to 2 (ca. 150 mL of 2 M HCl was added). The resulting mixture was diluted with 100 mL of satd NaCl solution, and the aqueous layer was separated and extracted with two 200-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 18.138 g of a dark yellow oil. Removal of triisopropylsilanol was achieved by four successive purifications via column chromatography on 150 g silica gel (elution with 5% EtOAc-hexanes-1% AcOH) to provide 2.135 g (23%) of acid **62** as a colorless oil: IR (neat) 3037, 2943, 2865, 2177, 1712, 1463, and 1433 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.86 (br s, 1H), 2.59 (m, 4H), 1.05 (d, J = 5.0 Hz, 18H), and 1.03 (sept, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 106.4, 81.8, 34.1, 18.7, 15.8, and 11.4; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{26}O_2Si$, 277.1594; found, 277.1593.

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with acid **62** (2.135 g, 8.391 mmol), 12 mL of toluene, and triethylamine (1.17 mL, 0.849 g, 8.39 mmol). Diphenylphosphoryl azide (1.81 mL, 2.31 g, 8.40 mmol) was added via syringe over 2 min, and the resulting solution was heated at 80 °C (bath temperature) until bubbling ceased (2 h). After the oil bath was warmed to 90 °C, *tert*-butanol (7.8 mL, 6.0 g, 84 mmol) was added and the resulting mixture was heated at reflux for 23 h. The solution was allowed to cool to room temperature, and the reaction mixture was concentrated onto 8 g of silica gel which was applied to a column of 180 g of silica gel (gradient elution with 2-20% EtOAc-hexanes) for purification to provide 0.838 g (31%) of carbamate **63** as a pale yellow oil: IR (neat) 3357, 2943, 2866, 2173, 1694, 1511, and 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.87 (br s, 1H), 3.25 (dt, J = 6.1, 6.6 Hz, 2H), 2.43 (t, J = 6.6 Hz, 2H), 1.42 (s, 9H), 1.04 (d, J = 5.0 Hz, 18H), and 1.03 (sept, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 105.8, 82.5, 79.4, 39.7, 28.5, 21.4, 18.8, and 11.4; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{35}NO_2Si$, 348.2329; found, 348.2314.



63 **64**

***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-(triisopropylsilyl)-3-butynylamine (64).** Reaction of a solution of carbamate **63** (0.253 g, 0.777 mmol) in 3.1 mL of pyridine with KHMDS (0.86 mL, 0.91 M in THF, 0.78 mmol), CuI (0.148 g, 0.777 mmol) in 1.6 mL of pyridine, and 1-bromo-2-(1-cyclohexenyl)ethyne[10] (2.6 mL, 0.60 M in benzene, 1.6 mmol) according to the general procedure gave 0.478 g of a dark red oil. Column chromatography on 40 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.160 g (48%) of ynamide **64** as a pale yellow oil: IR (neat) 2940, 2865, 2238, 2175, 1716, and 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (br s, 1H), 3.58 (t, J = 7.8 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H), 2.05-2.12 (m, 4H), 1.62 (m, 2H), 1.57 (m, 2H), 1.48 (s, 9H), 1.04 (d, J = 5.8 Hz, 18H), and 1.03 (sept, J = 5.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 131.5, 120.4, 104.5, 82.2, 82.2, 80.7, 72.3, 48.2, 29.5, 28.0, 25.6, 22.5, 21.7, 19.3, 18.6, and 11.3; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{43}NO_2Si$, 452.2955; found, 452.2958.

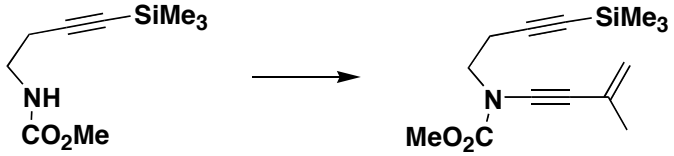


64 65 26

***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(1-cyclohexenyl)-ethynyl]-4-methoxycarbonyl-3-butnynlamine (26).** A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with silyl alkyne **64** (0.687 g, 1.60 mmol) and 50 mL of THF and cooled at 0 °C while 1.8 mL of *n*-Bu_4NF solution (1.0 M in THF, 1.8 mmol) was added via syringe. The resulting light brown solution was stirred at 0 °C for 20 min and then diluted with 50 mL of Et_2O and extracted with 50 mL of water. The aqueous layer was extracted with two 25-mL portions of Et_2O, and the combined organic layers were washed with 100 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.735 g of a deep yellow oil. Column chromatography on 60 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.345 g (79%) of desilylated alkyne **65** as a pale yellow oil: IR (neat) 3290, 2933, 2237, 2122, 1722, and 1449 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (br s, 1H), 3.57 (t, J = 7.5 Hz, 2H), 2.51 (dt, J = 2.7, 7.5 Hz, 2H), 2.04-2.10 (m, 4H), 1.96 (t, J = 2.7 Hz, 1H), 1.60 (m, 2H), 1.55 (m, 2H), and 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 131.8, 120.4, 82.4, 80.7, 80.6, 72.3, 70.1, 47.8, 29.6, 28.1, 25.7, 22.5, 21.7, and 18.0; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{23}NO_2$, 296.1621; found, 296.1625.

A 10-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with hexamethyldisilazane (0.37 mL, 0.28 g, 1.8 mmol) and 3 mL of THF. The solution was cooled at 0 °C while 0.68 mL of *n*-BuLi solution (2.40 M in hexanes, 1.6 mmol) was added via syringe over 2 min and allowed to stir at 0 °C for 30 min. A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **65** (0.345 g, 1.26 mmol) and 9 mL of THF. The solution was cooled at -78 °C while the LiHMDS solution prepared as described above was added via cannula over 3 min (0.6-mL THF rinse). The resulting yellow solution was stirred at -78 °C for 2 h. Methyl chloroformate (0.97 mL, 1.2 g, 13 mmol) was added in one portion via syringe, and the reaction mixture was stirred at -78 °C for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0 °C for 1 h and then diluted with 60 mL of Et_2O. The solution was extracted with

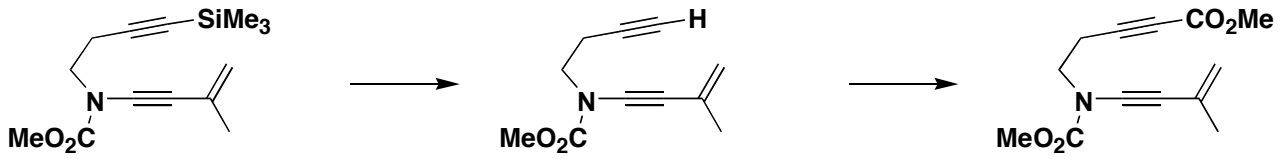
30 mL of a 2:1 mixture of conc NH_4OH solution and satd NaCl solution, and the aqueous layer was extracted with two 20-mL portions of Et_2O. The combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.965 g of a mixture of yellow oil and white needles. Column chromatography on 90 g silica gel (elution with 5% EtOAc-hexanes) provided 0.249 g (60%) of ynamide **26** as a colorless oil: IR (neat) 2933, 2241, 1720, and 1435 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (br s, 1H), 3.65 (s, 3H), 3.56 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.00 (m, 4H), 1.55 (m, 2H), 1.49 (m, 2H), and 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 153.5, 131.9, 120.1, 85.4, 82.5, 80.2, 74.0, 72.4, 52.5, 46.8, 29.4, 27.9, 25.5, 22.3, 21.6, and 18.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{25}NO_4$, 354.1676; found, 354.1679.



56 **27**

***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-4-(trimethylsilyl)-3-butynylamine (27).** Reaction of a solution of carbamate **56** (0.959 g, 4.81 mmol) in 19 mL of pyridine with KHMDS (5.3 mL, 0.91 M in THF, 4.8 mmol), CuI (0.918 g, 4.82 mmol) in 10 mL of pyridine, and 1-bromo-3-methyl-3-buten-1-yne[11] (17 mL, 0.58 M in benzene, 9.6 mmol) according to the general procedure gave 1.425 g of a dark red oil. Column chromatography on 120 g of silica gel (gradient elution with 0-2% EtOAc-hexanes) provided 0.579 g (46%) of ynamide **27** as a yellow oil: IR (neat) 2957, 2236, 2179, 1736, 1613, and 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 5.14 (s, 1H), 3.81 (s, 3H), 3.65 (t, J = 7.5 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 1.90 (s, 3H), and 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 126.3, 119.7, 102.6, 86.8, 81.7, 72.2, 54.2, 49.0, 23.8, 19.3, and 0.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{21}NO_2Si$, 286.1234; found, 286.1239.

[11] Prepared from 2-methyl-1-buten-3-yne, NBS, and catalytic $AgNO_3$ according to the procedure of Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.

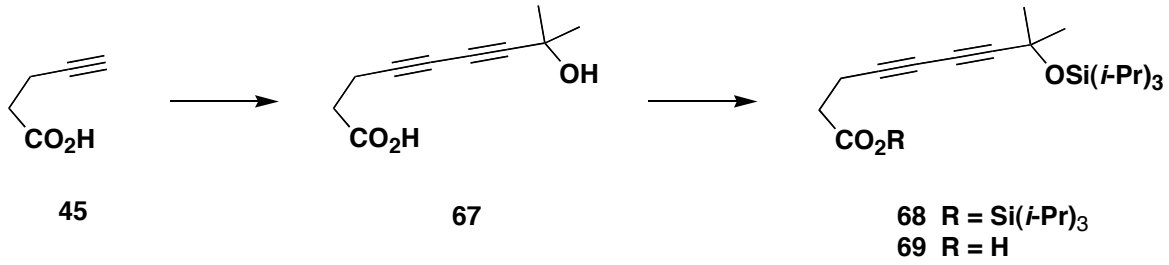


27 **66** **28**

***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-4-methoxycarbonyl-3-butnynlamine (28).** A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with silyl alkyne **27** (0.256 g, 0.972 mmol) and 20 mL of THF and cooled at 0 °C while 1.1 mL of *n*-Bu_4NF solution (1.0 M in THF, 1.1 mmol) was added via syringe. The resulting yellow solution was stirred at 0 °C for 15 min and then diluted with 20 mL of Et_2O and extracted with 20 mL of water. The aqueous layer was extracted with two 10-mL portions of Et_2O, and the combined organic layers were washed with 25 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.188 g of a dark red oil. Column chromatography on 30 g silica gel (elution with 5% EtOAc-hexanes) provided 0.154 g (83%) of desilylated alkyne **66** as a pale yellow oil: IR (neat) 3293, 2956, 2236, 2122, 1731, 1613, and 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (s, 1H), 5.12 (s, 1H), 3.79 (s, 3H), 3.65 (t, J = 7.3 Hz, 2H), 2.54 (dt, J = 2.6, 7.3 Hz, 2H), 2.00 (t, J = 2.6 Hz, 1H), and 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 126.3, 119.9, 81.5, 80.3, 72.3, 70.3, 54.3, 48.8, 23.7, and 17.9; GC-MS *m/z*: 191 (M^+).

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alkyne **66** (0.151 g, 0.790 mmol) and 7.9 mL of THF. The solution was cooled at -78 °C while 1.0 mL of LiHMDS solution (1.03 M in THF, 1.0 mmol) was added via syringe over 1 min, and the resulting yellow solution was stirred at -78 °C for 90 min. Methyl chloroformate (0.60 mL, 0.75 g, 7.9 mmol) was added in one portion via syringe, and the reaction mixture was stirred at -78 °C for 3 h. The dry ice-acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0 °C for 1 h and then diluted with 30 mL of Et_2O. The solution was extracted with 15 mL of a 2:1 mixture of conc NH_4OH solution and satd NaCl solution, and the aqueous layer was extracted with two 10-mL portions of Et_2O. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.375 g of a mixture of yellow oil and white needles. Column chromatography on 30 g silica gel (elution with 15% EtOAc-hexanes) provided 0.134 g (68%) of ynamide **28** as a colorless oil: IR (neat) 2956, 2241, 2154, 1729, 1692, 1613, and 1440 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 5.16 (s, 1H), 5.11 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.68 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), and 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 153.8, 126.1, 120.1, 85.0, 81.1, 74.3, 72.4, 54.3, 52.7, 47.9, 23.6, and 18.2; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}NO_4$, 250.1074; found, 250.1069.



45 **67** **68 R = Si(*i*-Pr)$_3$** **69 R = H**

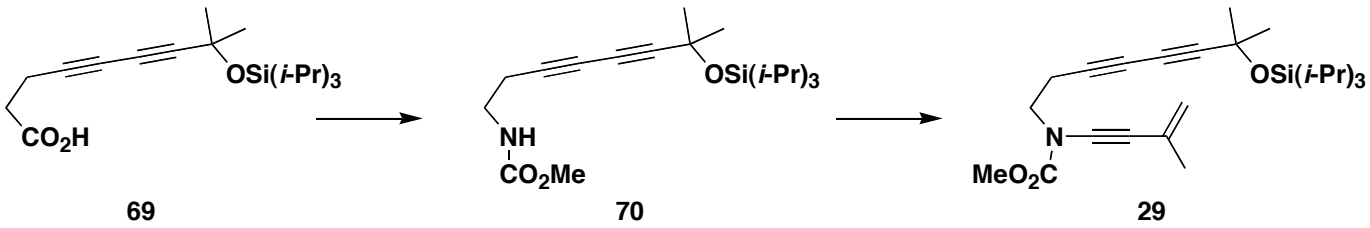
8-(Triisopropylsiloxy)-8-methyl-nona-4,6-diynoic acid (69). A 200-mL, three-necked, round-bottomed flask equipped with two glass stoppers and an addition funnel fitted with an argon inlet adapter was charged with CuCl (0.023 g, 0.23 mmol), NH_2OH•HCl (0.112 g, 1.61 mmol), 22 mL of methanol, and 20 mL of aqueous ethylamine (70% wt in H_2O) solution. The reaction mixture was cooled at 0 °C while 4-pentynoic acid (**45**) (4.350 g, 44.34 mmol) was added in one portion. 1-Bromo-3-hydroxy-3-methylbutyne[8] (6.896 g, 42.30 mmol) was added dropwise via the addition funnel over 15 min, and the resulting pale yellow solution was stirred at 0 °C for 20 min. The solution was diluted with 100 mL of water, 20 mL of conc HCl, and extracted with twenty-five 50-mL portions of CH_2Cl_2. The combined organic phases were concentrated to a volume of ca. 150 mL, washed with 100 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 6.164 g of a white solid. Trituration of the crude material with two 150-mL portions of hexanes (heated to boiling point) afforded 3.040 g (40%) of diynoic acid **67** as a white solid: mp 129-131 °C (lit.[12] mp 132 °C); IR (film) 3406, 2983, 2255, 1726, and 1363 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.13 (br s, 1H), 3.49 (br s, 1H), 2.52 (m, 4H), and 1.42 (s, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ 173.5, 82.9, 81.3, 67.0, 65.8, 65.5, 33.2, 31.7, and 15.9; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{12}O_3$, 203.0679; found, 203.0684.

A 50-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with acid **67** (1.550 g, 8.602 mmol) and 25 mL of CH_2Cl_2. The resulting suspension

[12] Prevost, S.; Meier, J.; Chodkiewicz, W.; Cadiot, P.; Willemart, A. *Bull. Soc. Chim. Fr.* **1961**, 2171.

was cooled at 0 °C while 2,6-lutidine (3.0 mL, 2.7 g, 26 mmol) was added in one portion via syringe, and the resulting homogeneous solution was treated with triisopropylsilyl triflate (5.8 mL, 6.6 g, 22 mmol) via syringe over 3 min. The ice bath was removed and the reaction mixture was allowed to stir at rt for 18 h. The resulting solution was diluted with 50 mL of Et_2O, washed with 20 mL of water, 20 mL of 3% HCl, and 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 4.832 g of **68** as a yellow oil.

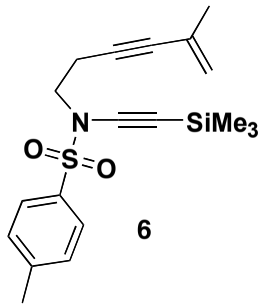
A 100-mL, round-bottomed flask equipped with an argon inlet adapter was charged with a solution of **68** in 35 mL of methanol, 10 mL of THF, and 10 mL of water. Potassium carbonate (5.9 g, 43 mmol) was added in one portion, and the reaction mixture was vigorously stirred for 1 h. The resulting suspension was diluted with 100 mL of CH_2Cl_2 and 20 mL of satd NaCl solution, and 10% HCl was added dropwise to adjust the pH to 2 (ca. 55 mL of 10% HCl was added). The resulting mixture was diluted with 20 mL of satd NaCl solution, and the aqueous layer was separated and extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 4.766 g of a yellow oil. Column chromatography on 140 g of silica gel (elution with 15% EtOAc-hexanes containing 0.1% AcOH) provided 2.688 g (93% overall from **67)** of acid **69** as white solid: mp 49-50 °C; IR (film) 3037, 2944, 2867, 2255, 1715, 1463, and 1432 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.88 (br s, 1H), 2.64 (m, 4H), 1.53 (s, 6H), 1.13 (sept, J = 6.6 Hz, 3H), and 1.08 (d, J = 6.6 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 81.9, 78.4, 67.6, 66.6, 65.7, 33.1, 33.0, 18.5, 15.2, and 13.2; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{32}O_3Si$, 359.2013; found, 359.2007.



***N*-(Methoxycarbonyl)-*N*-(3-methyl-3-buten-1-ynyl)-7-(triisopropylsiloxy)-7-methyl-octa-3,5-diynylamine (29).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and reflux condenser fitted with an argon inlet adapter was charged with acid **69** (1.068 g, 3.173 mmol), 4.6 mL of toluene, and triethylamine (0.45 mL, 0.33 g, 3.2 mmol). Diphenylphosphoryl azide (0.69 mL, 0.88

g, 3.2 mmol) was added via syringe over 1 min, and the resulting solution was heated at 80 °C (bath temperature) until bubbling ceased (2 h). The oil bath was cooled to 50 °C, methanol (1.3 mL, 1.0 g, 32 mmol) was added, and the resulting mixture was stirred at 50 °C for 13 h. The resulting mixture was allowed to cool to room temperature and the toluene and methanol were removed by rotary evaporation at rt and 20 mmHg. The resulting orange-brown oil was diluted with 20 mL of Et_2O and 20 mL of water, and the aqueous phase was extracted with four 100-mL portions of Et_2O. The combined organic phases were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.142 g of a pale orange solid. Column chromatography on 80 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 1.009 g (87%) of carbamate **70** as a white solid: mp 55-56 °C; IR (film) 3306, 2944, 2866, 2249, 1692, 1563, and 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (br s, 1H), 3.68 (s, 3H), 3.34 (app q, J = 6.4 Hz, 2H), 2.51 (t, J = 6.4 Hz, 2H), 1.52 (s, 6H), 1.12 (sept, J = 6.4 Hz, 3H), and 1.07 (d, J = 6.4 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 81.8, 78.0, 67.5, 66.6, 66.4, 52.4, 39.7, 33.1, 21.1, 18.5, and 13.1; HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{35}NO_3Si$, 388.2278; found, 388.2267.

Reaction of a solution of carbamate **70** (0.495 g, 1.35 mmol) in 5.4 mL of pyridine with KHMDS (1.5 mL, 0.90 M in THF, 1.4 mmol), CuI (0.258 g, 1.35 mmol) in 2.7 mL of pyridine, and 1-bromo-3-methyl-3-buten-1-yne[11] (4.5 mL, 0.60 M in benzene, 2.7 mmol) according to the general procedure gave 0.599 g of a dark red oil. Column chromatography on 35 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.386 g (67%) of ynamide **29** as a pale yellow oil: IR (film) 2944, 2866, 2237, 1736, 1615, and 1446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.14 (s, 1H), 3.80 (s, 3H), 3.66 (t, J = 7.3 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 1.90 (s, 3H), 1.50 (s, 6H), 1.12 (sept, J = 7.0 Hz, 3H), and 1.06 (d, J = 7.0 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 126.3, 120.0, 81.7, 81.4, 76.6, 72.5, 67.6, 66.6, 66.6, 54.3, 48.7, 33.1, 23.8, 19.0, 18.4, and 13.1; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{25}H_{39}NO_3Si$, 430.2772; found, 430.2779.



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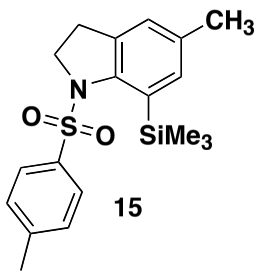

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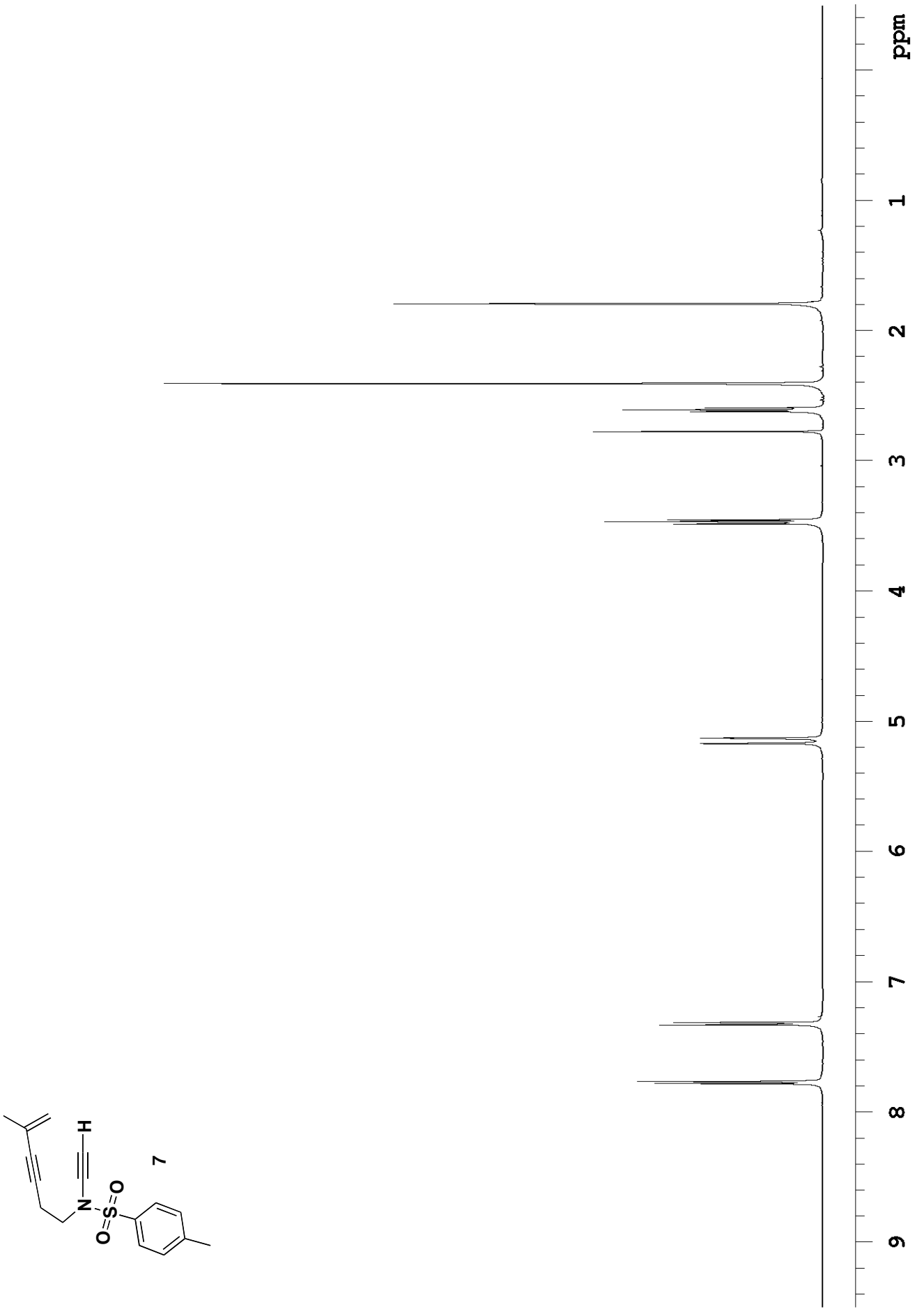
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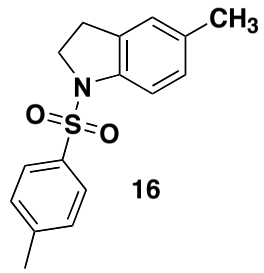

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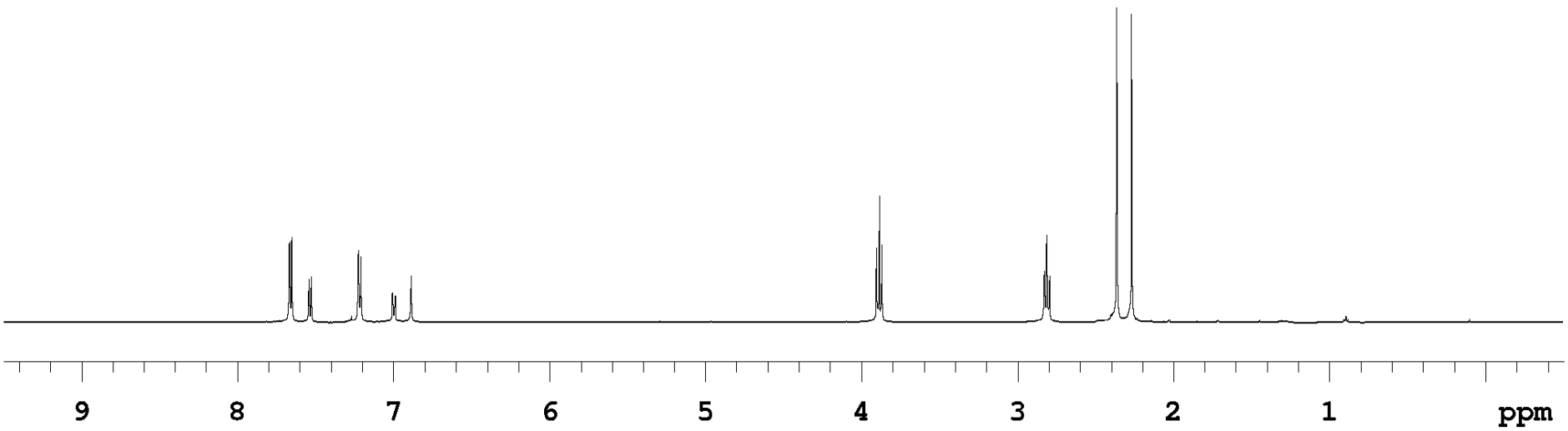

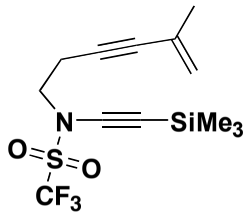

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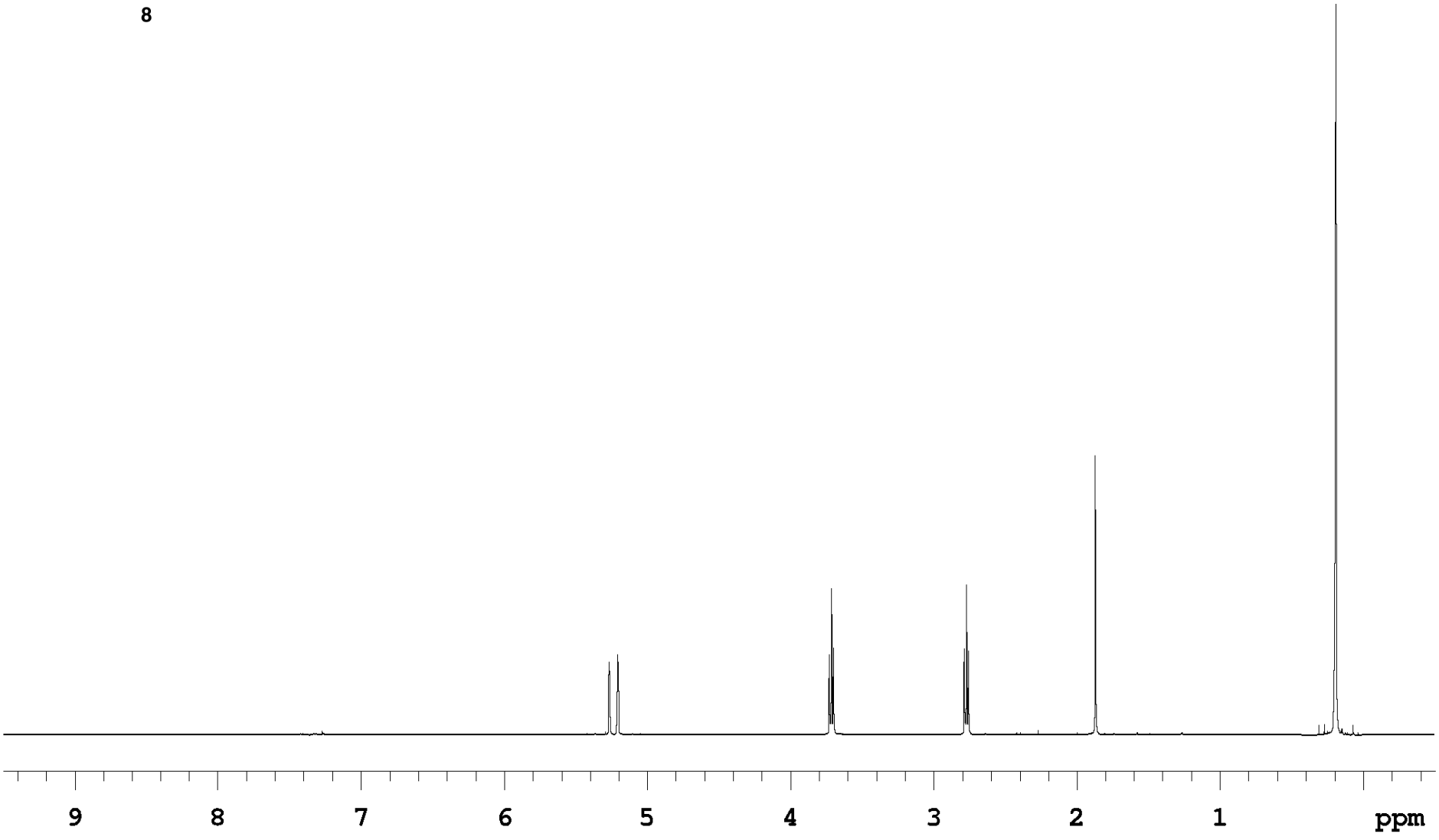

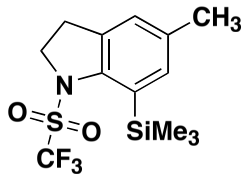

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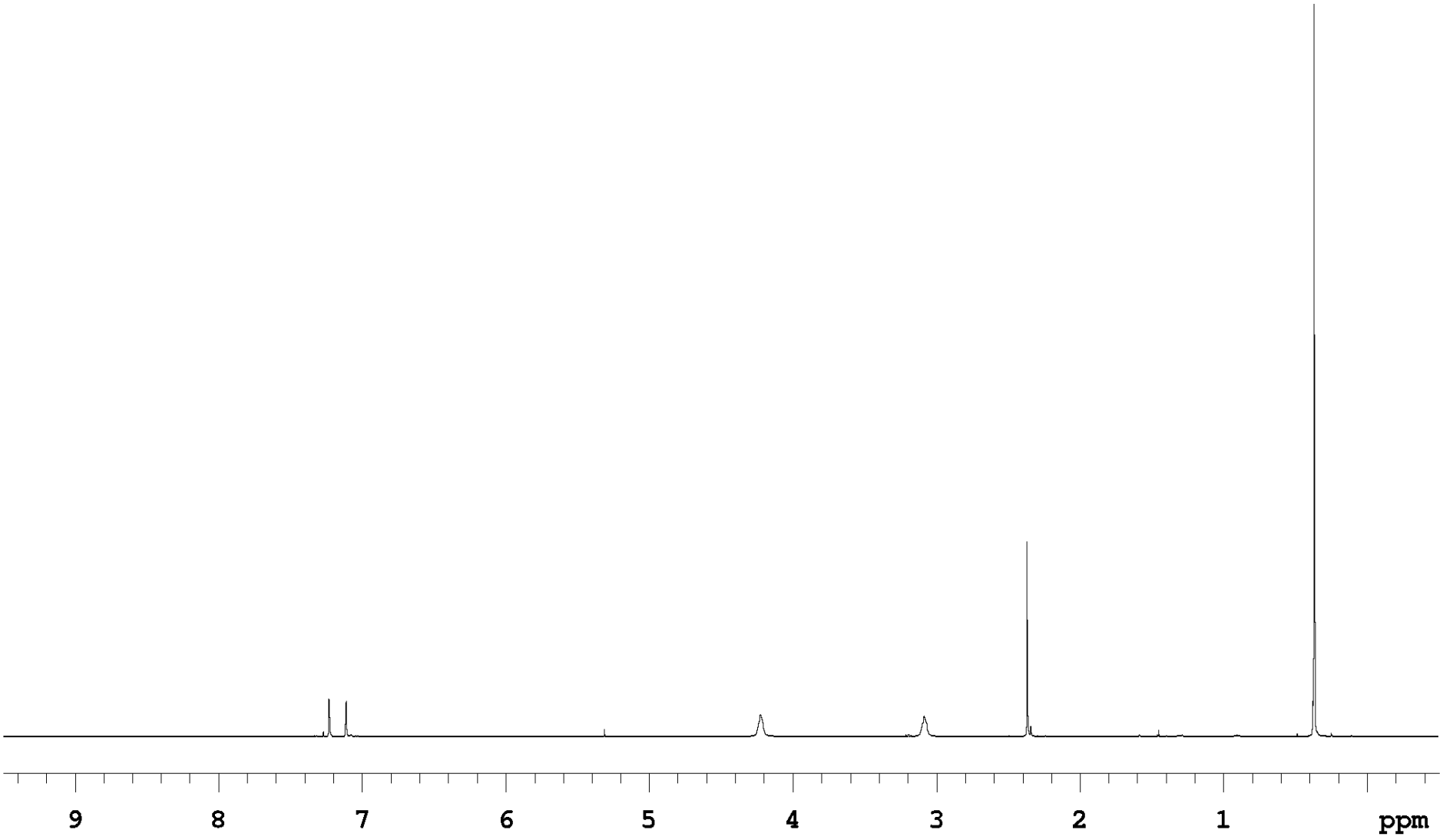

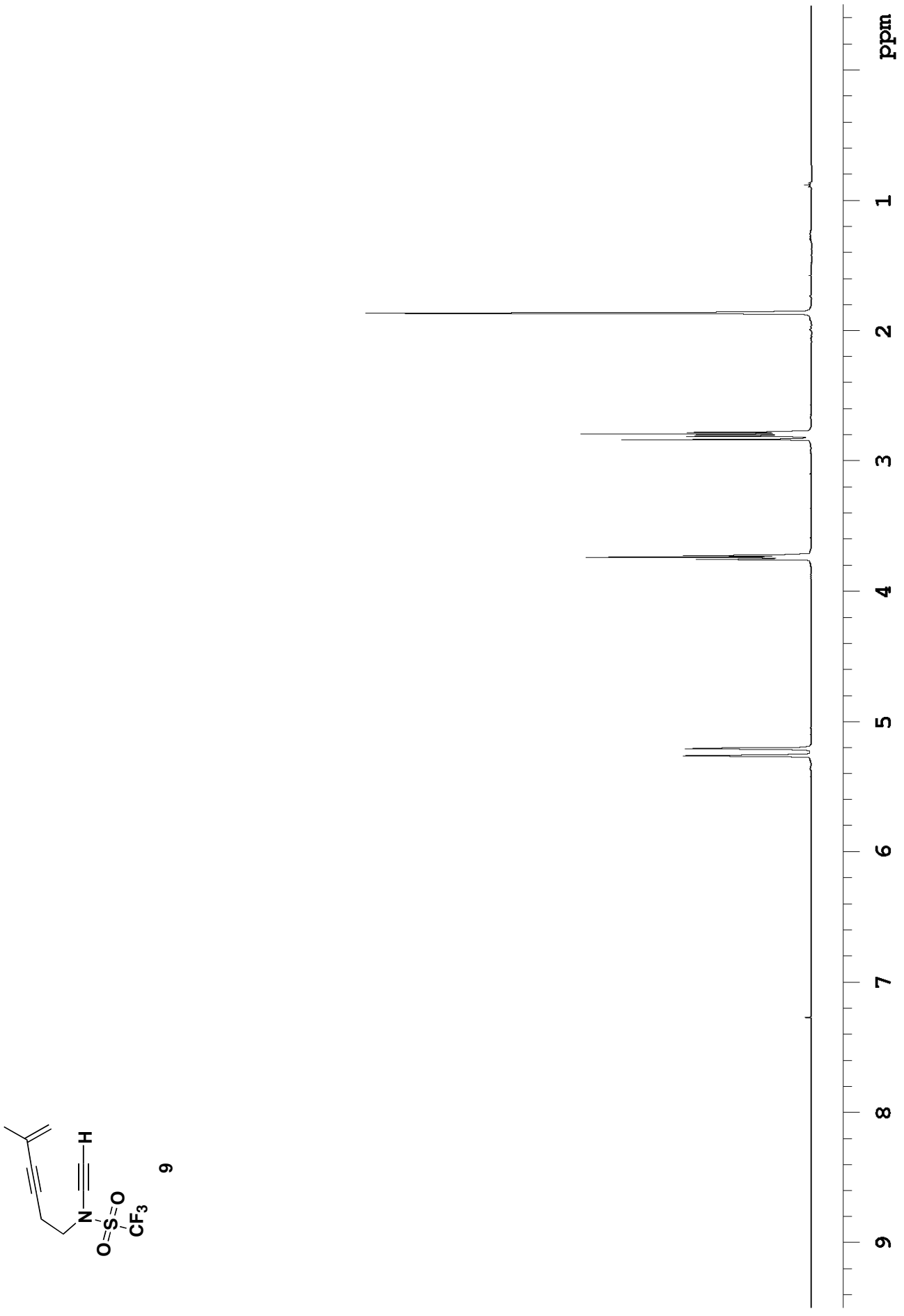

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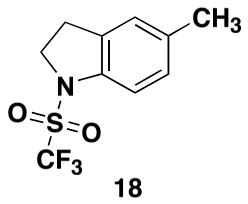

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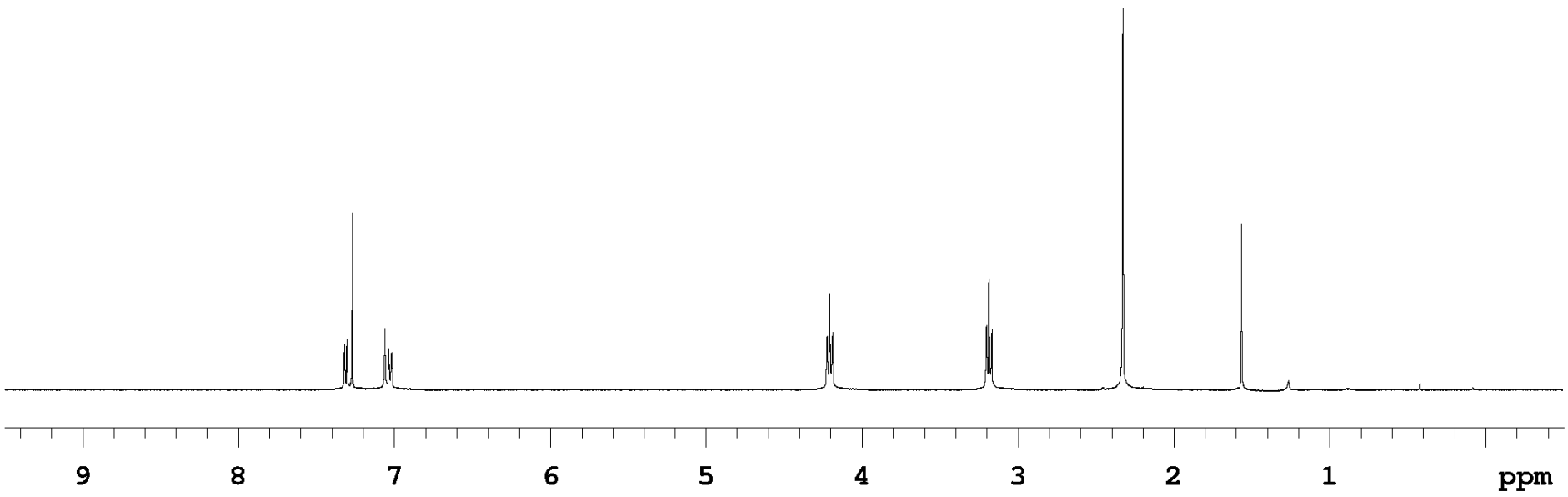

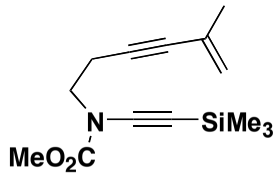

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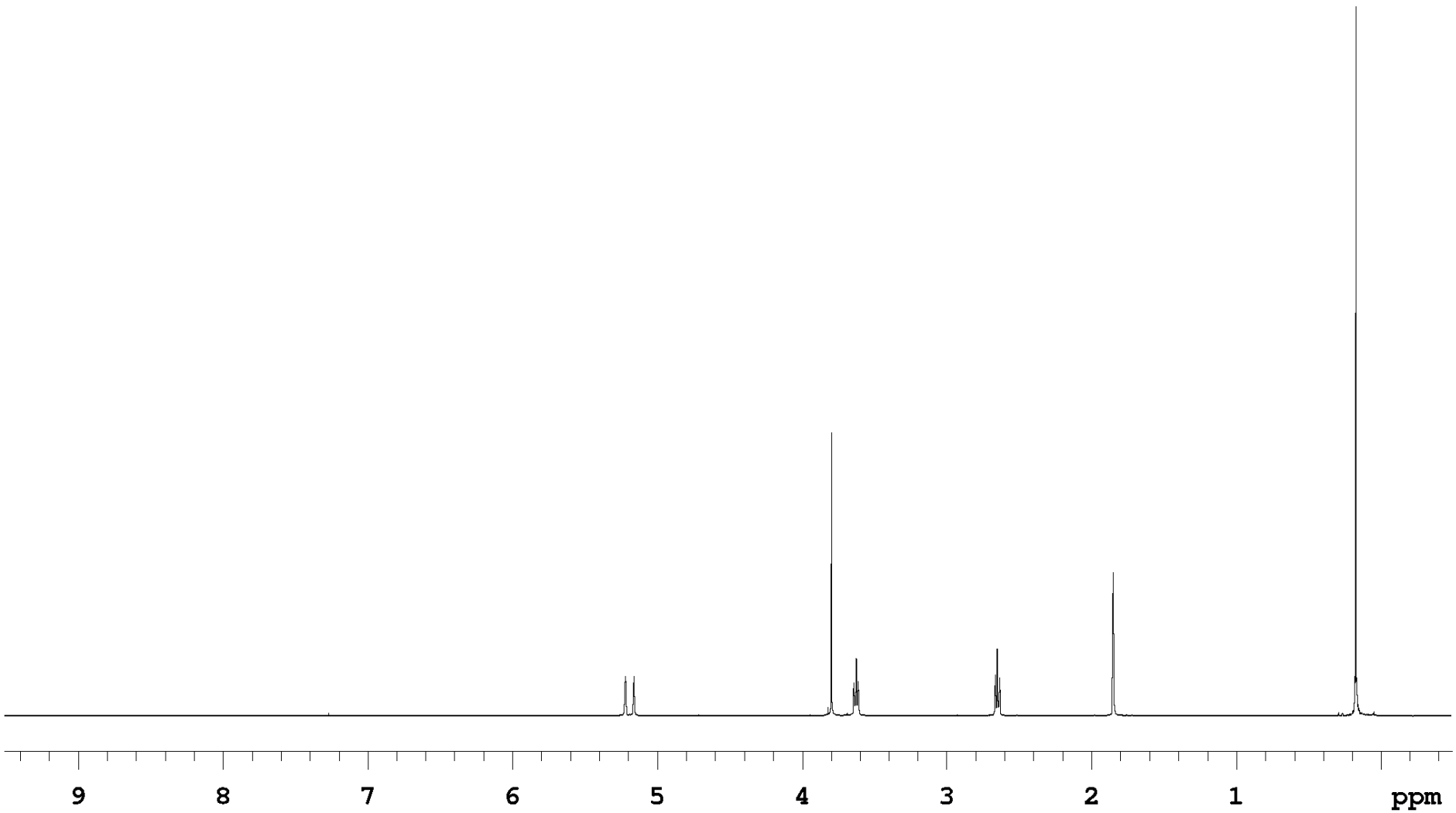

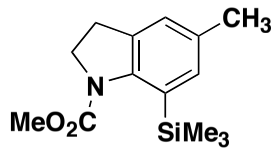

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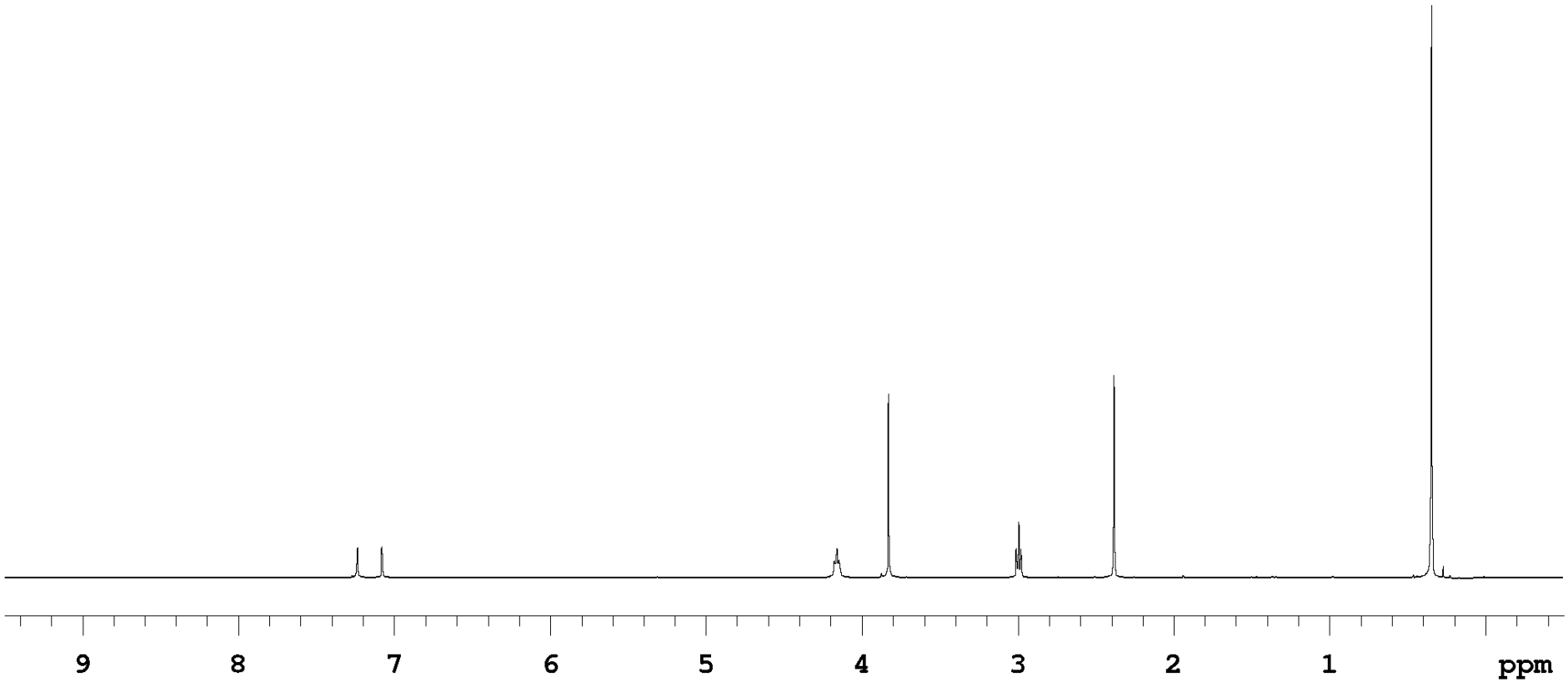

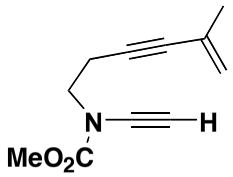

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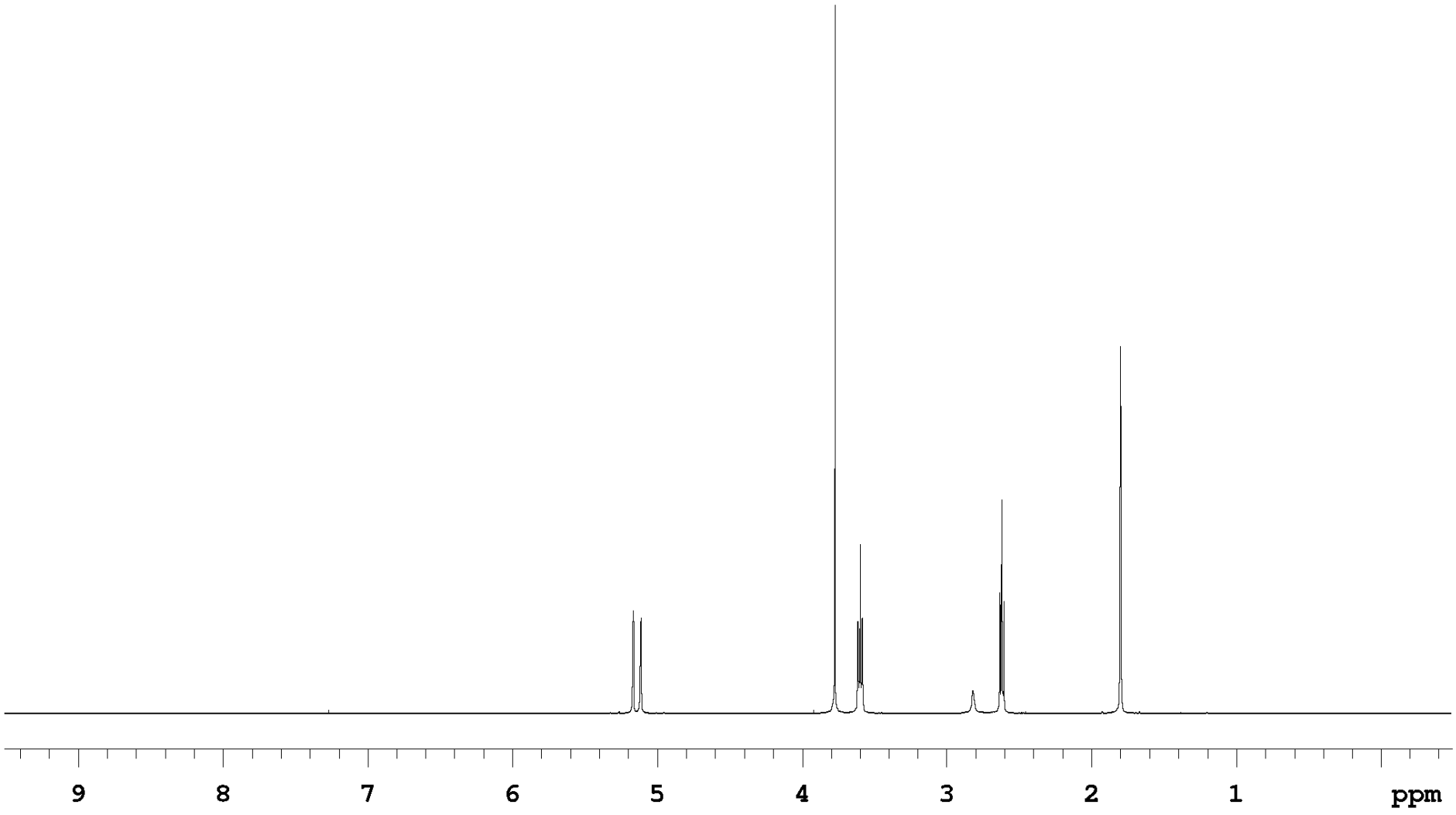

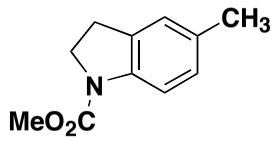

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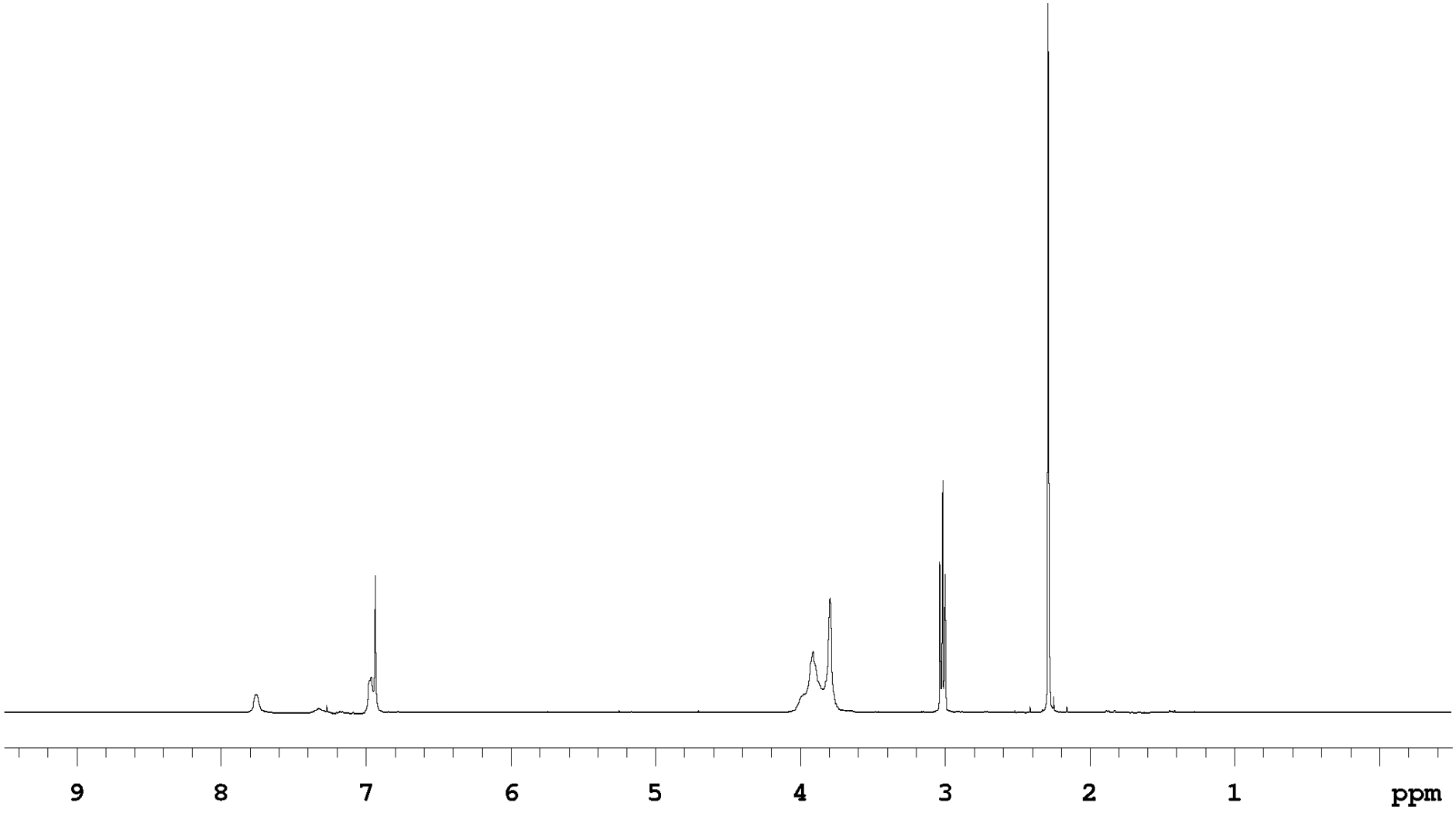

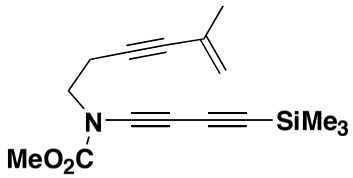

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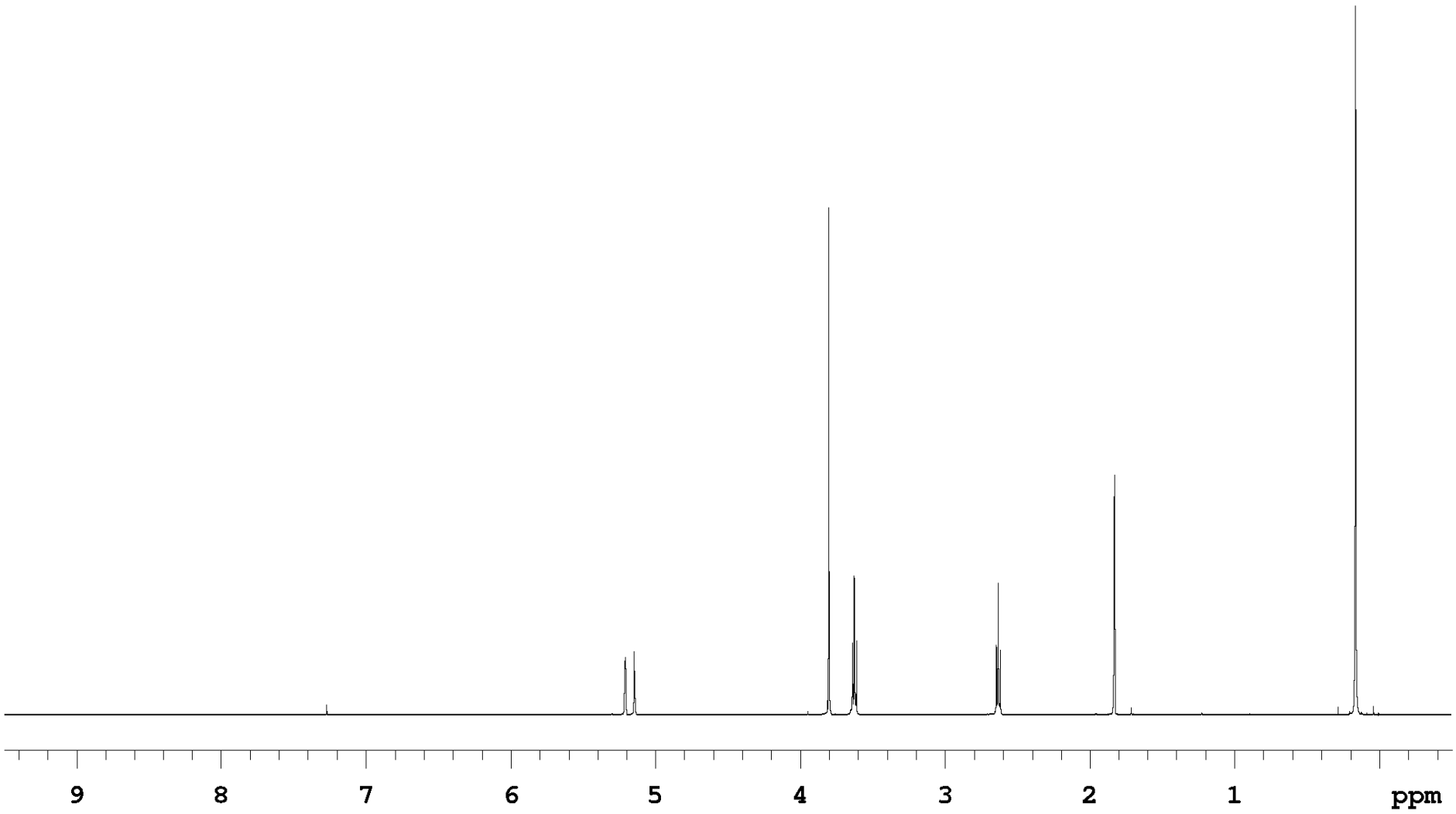

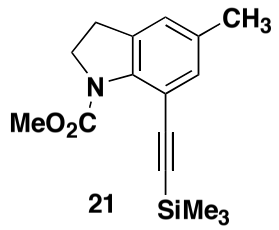
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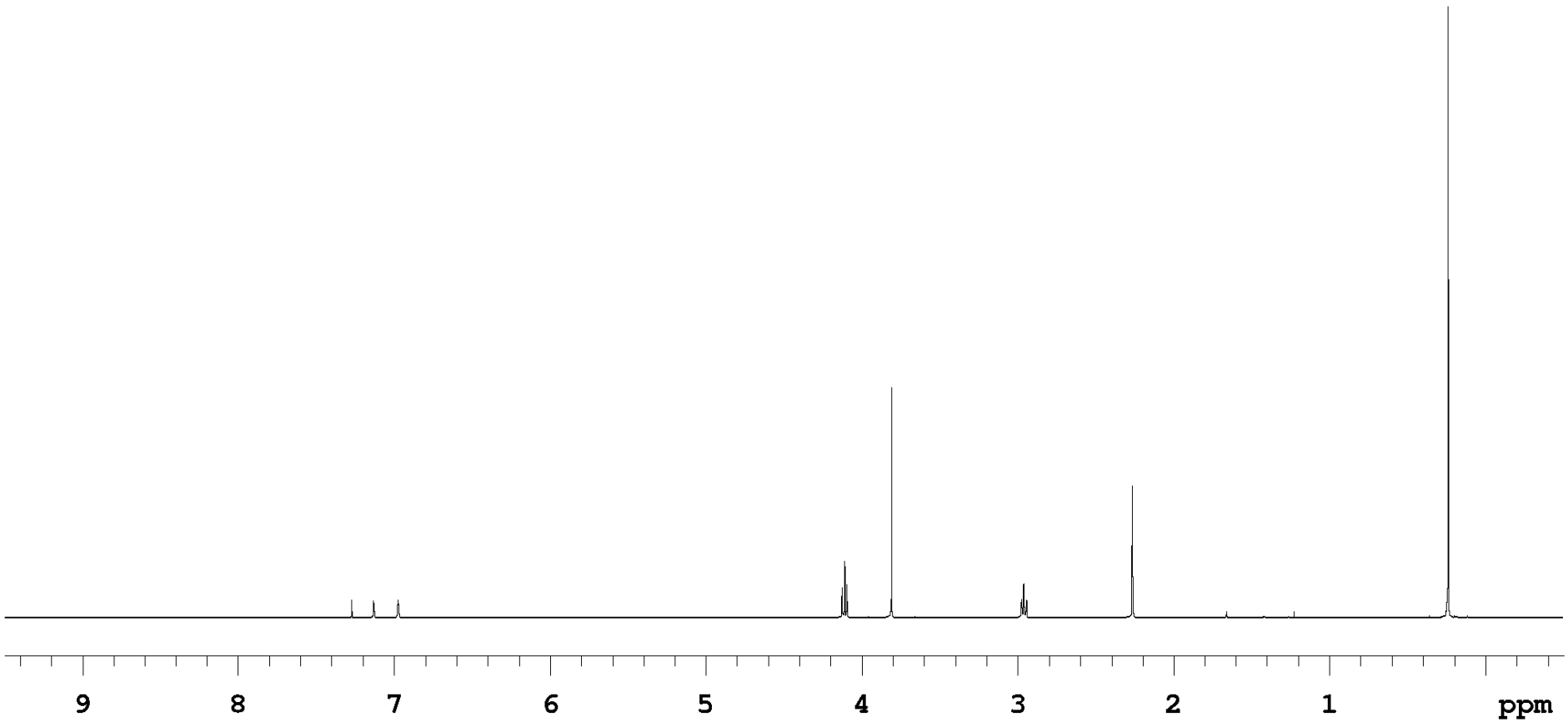
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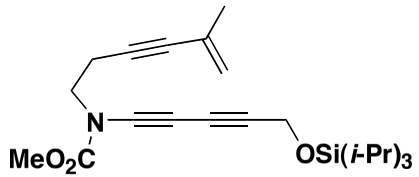

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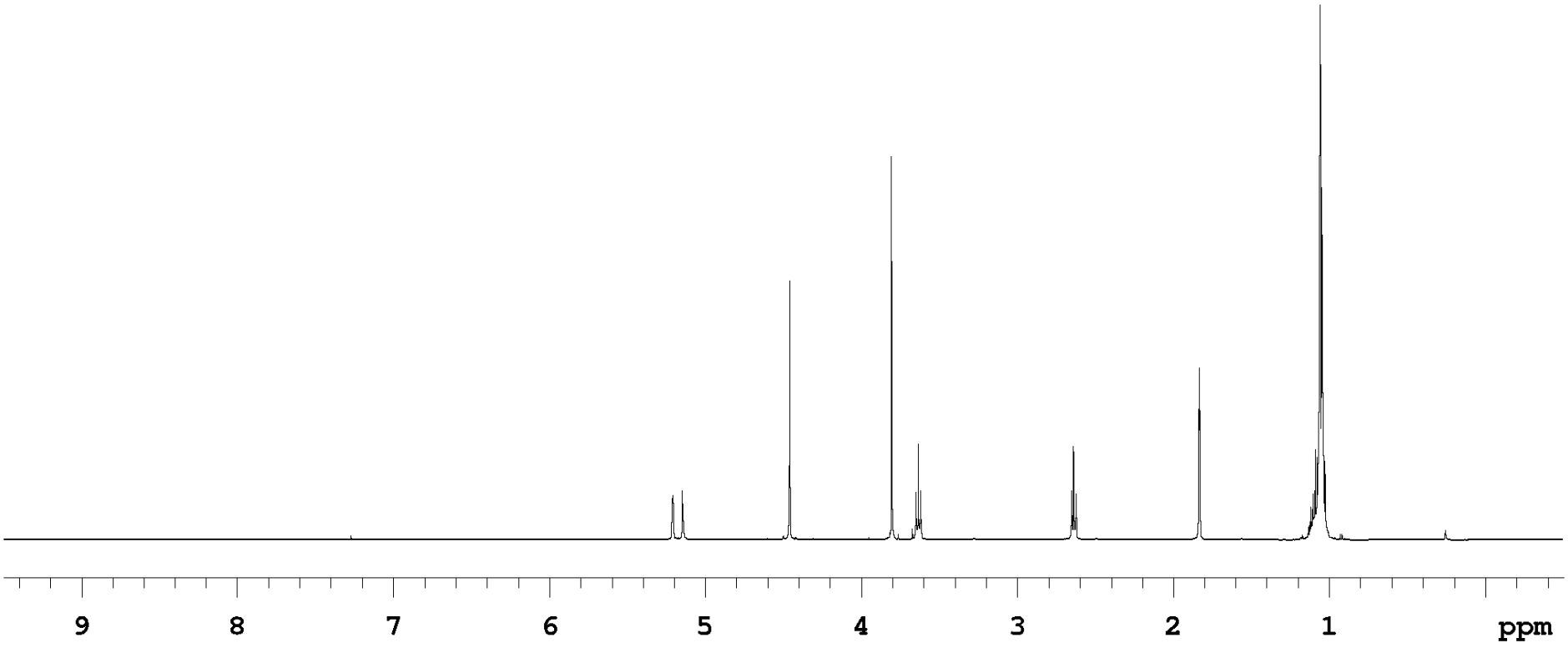

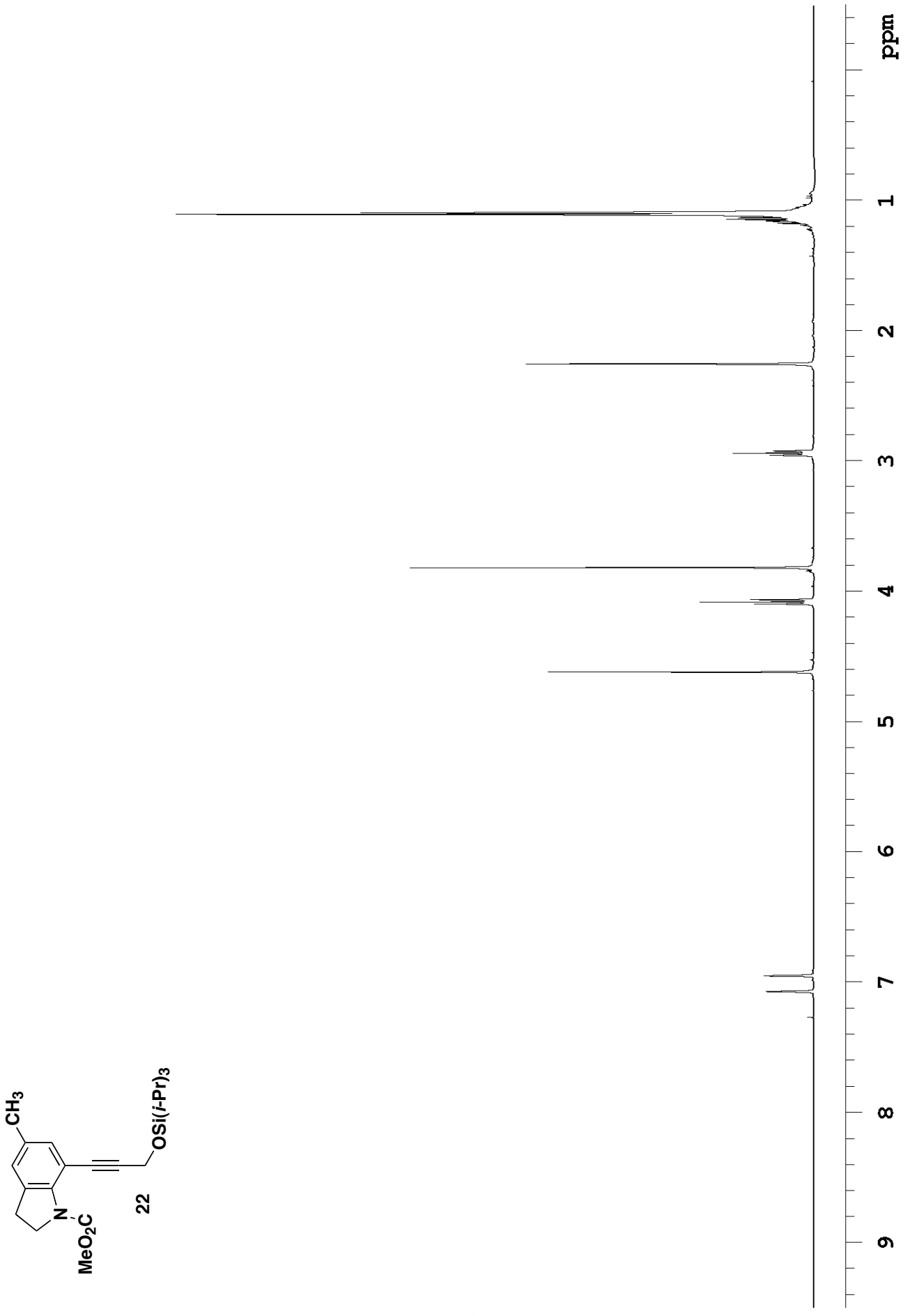
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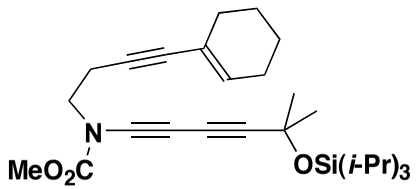

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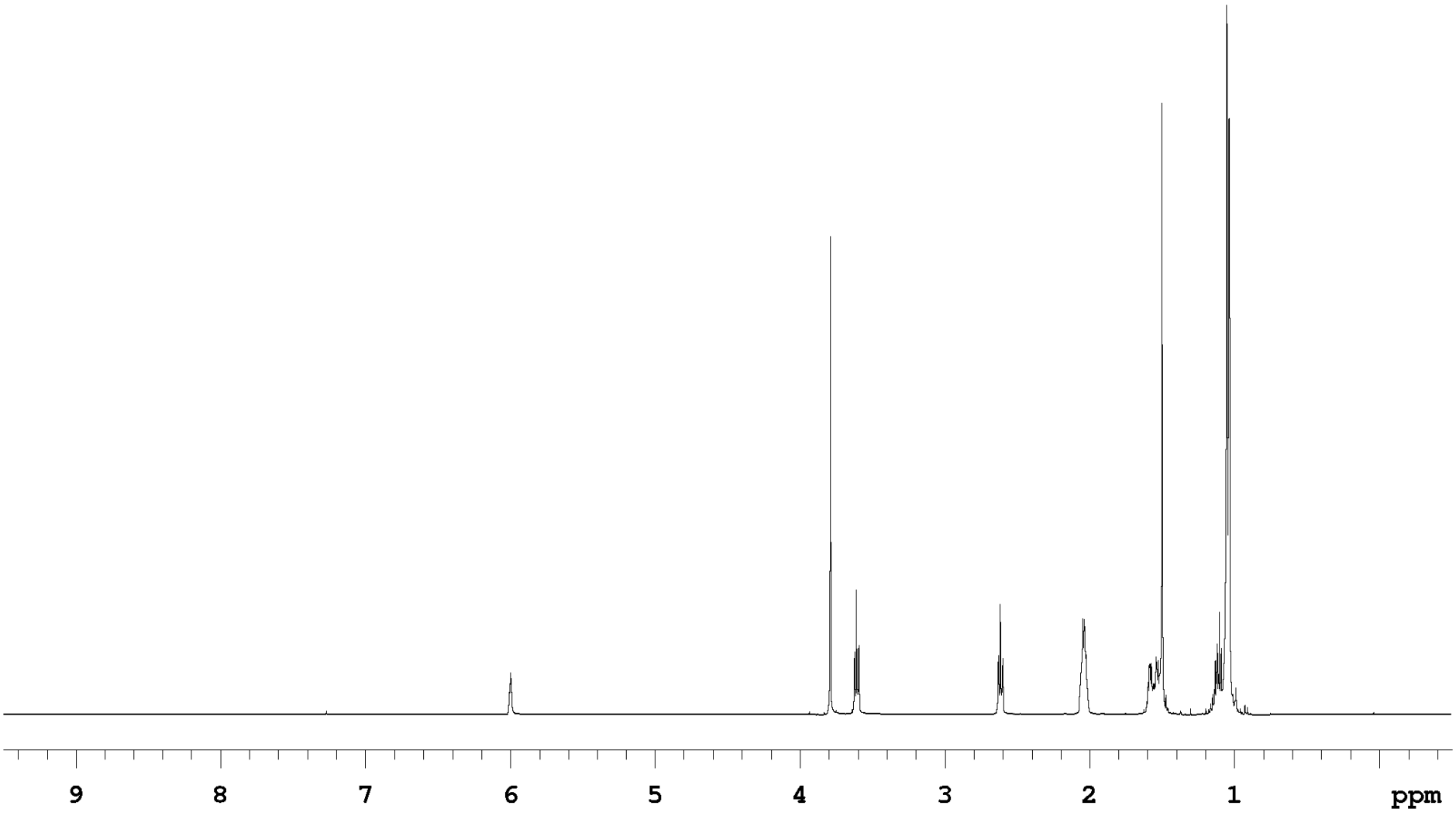

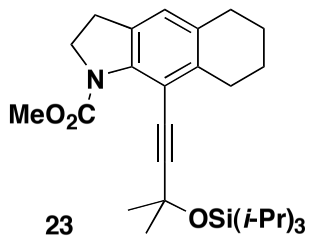

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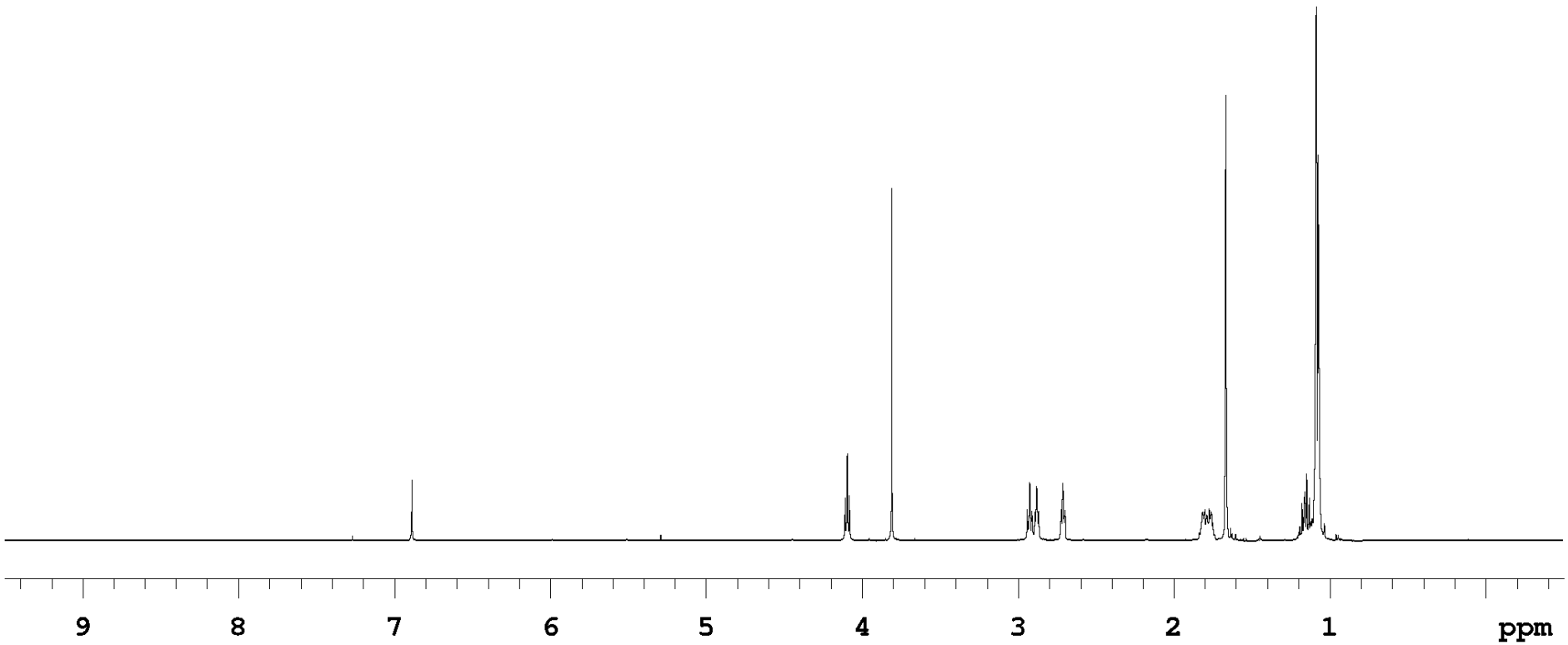

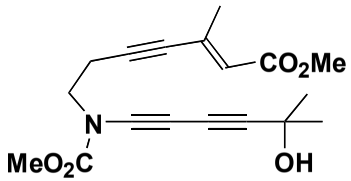

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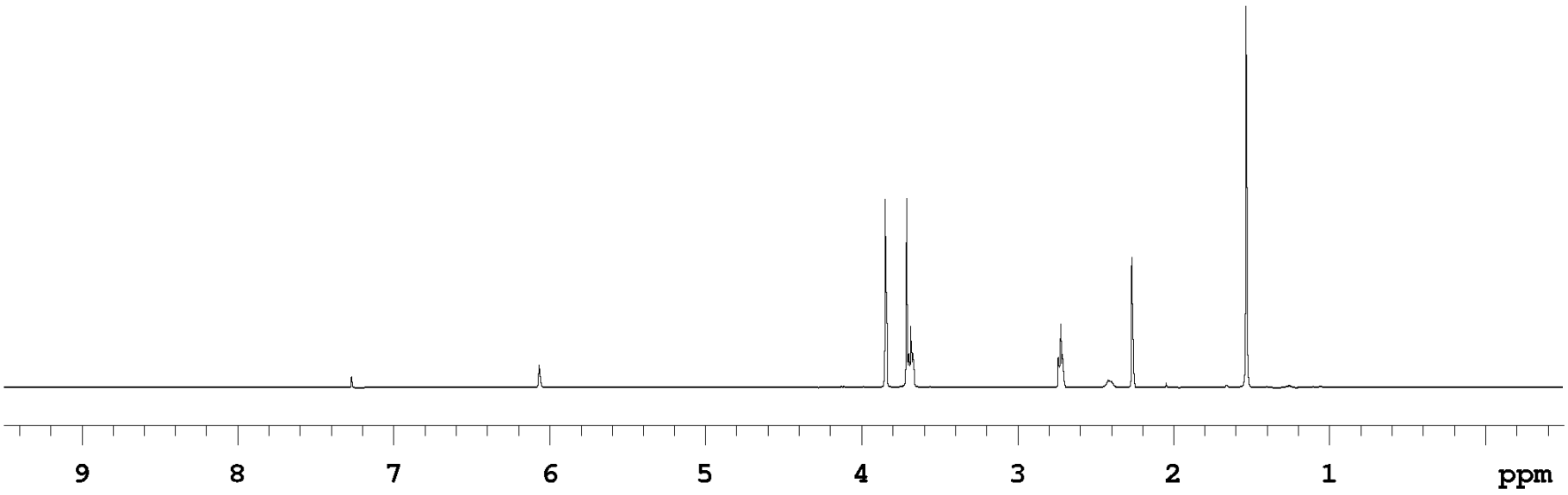

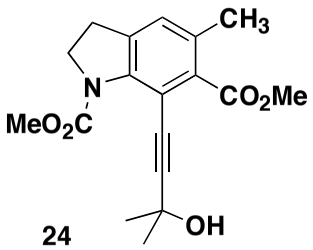

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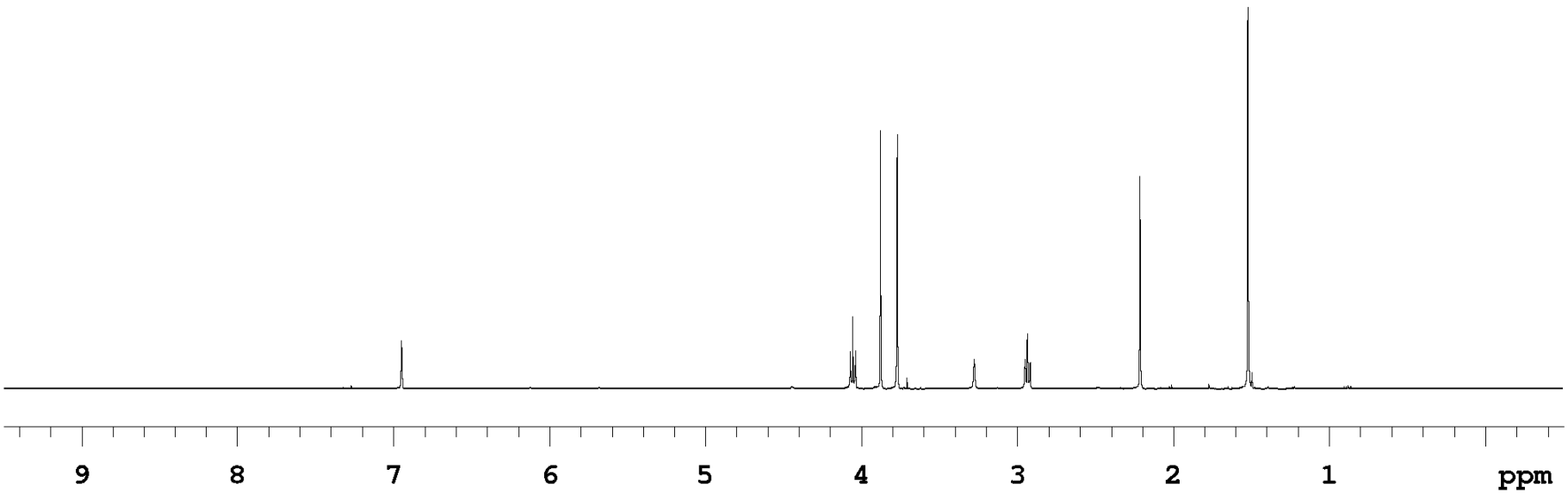

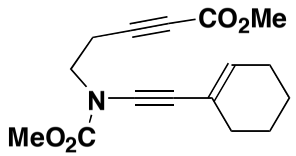

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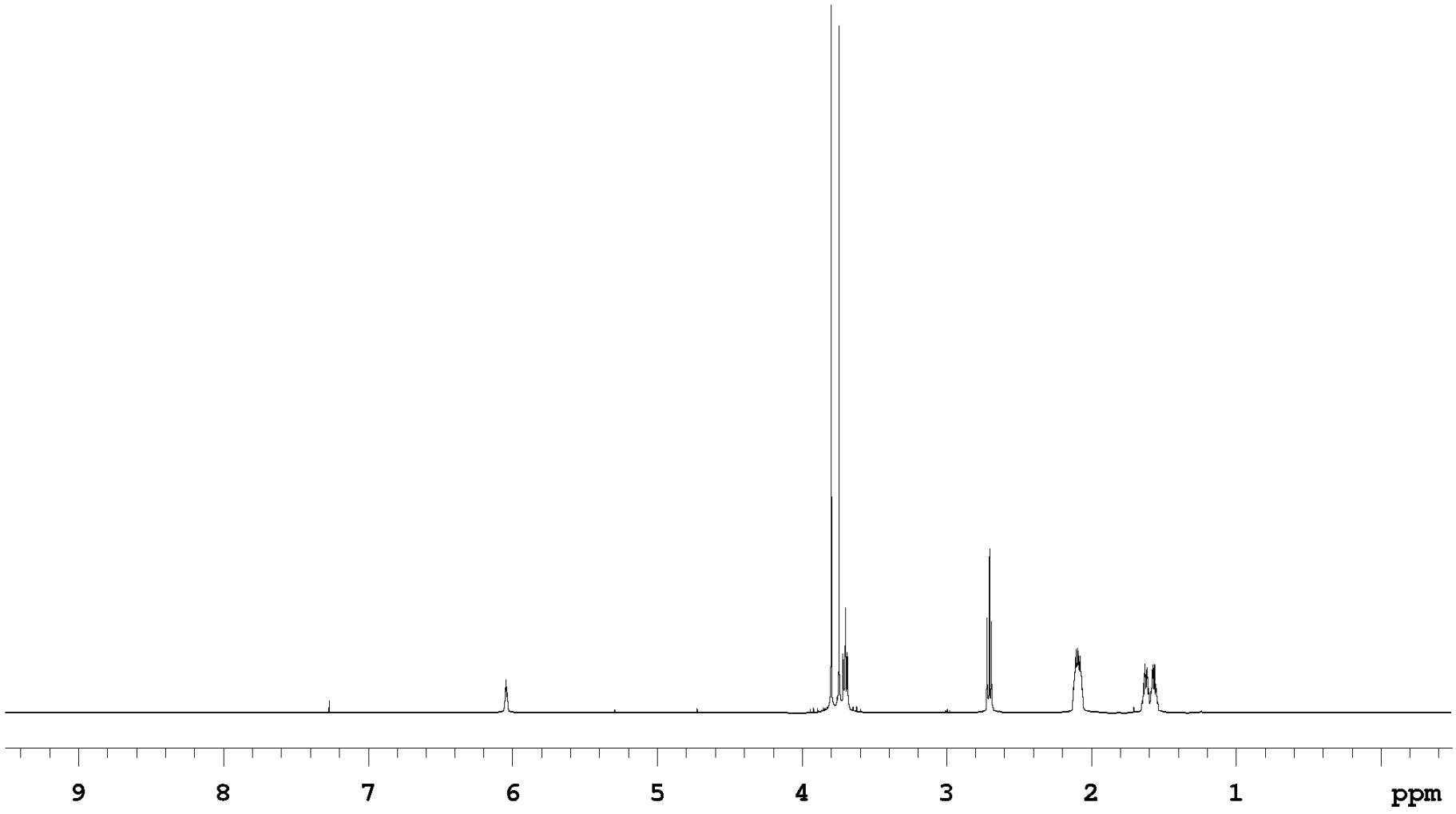

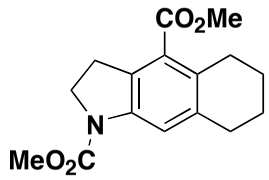

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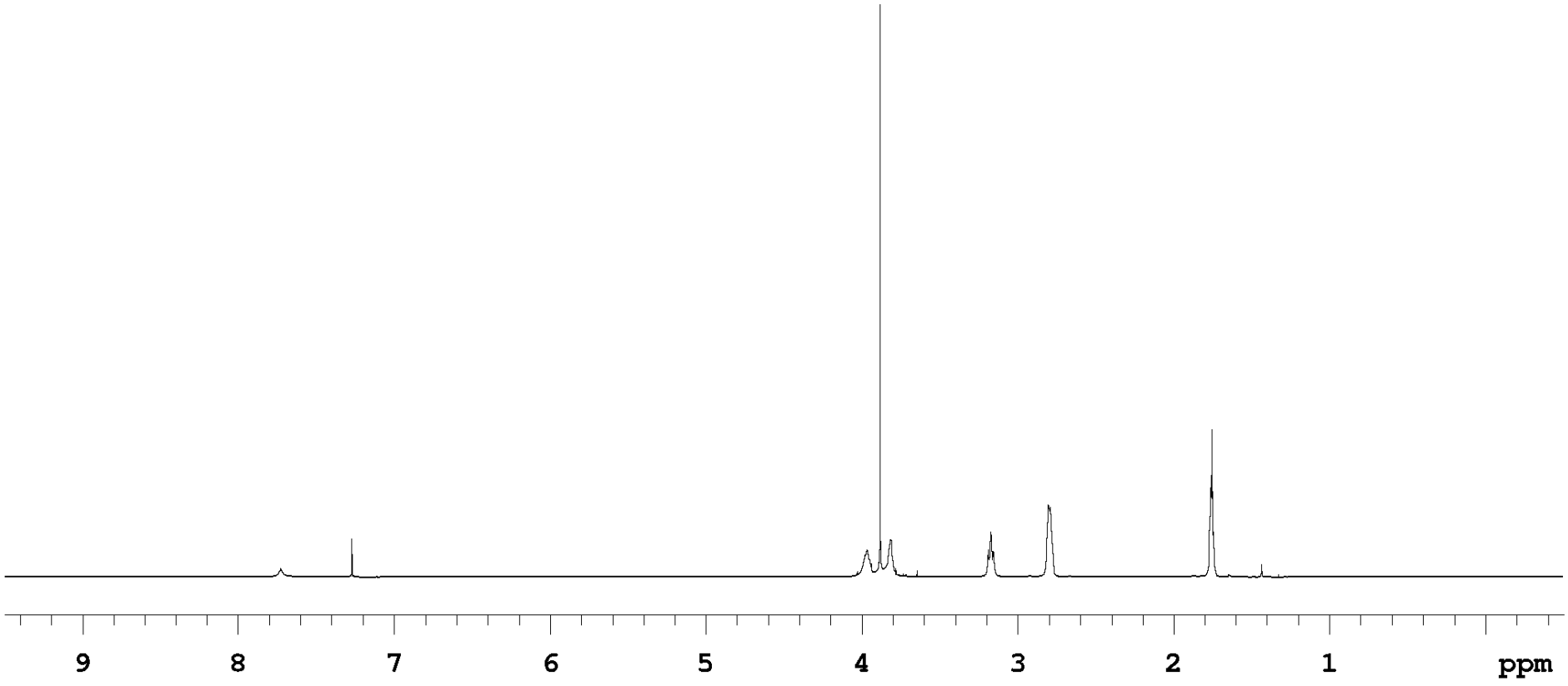

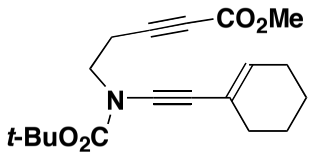

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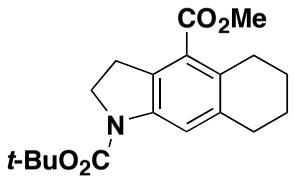

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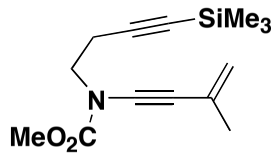

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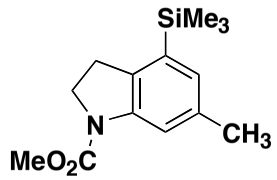

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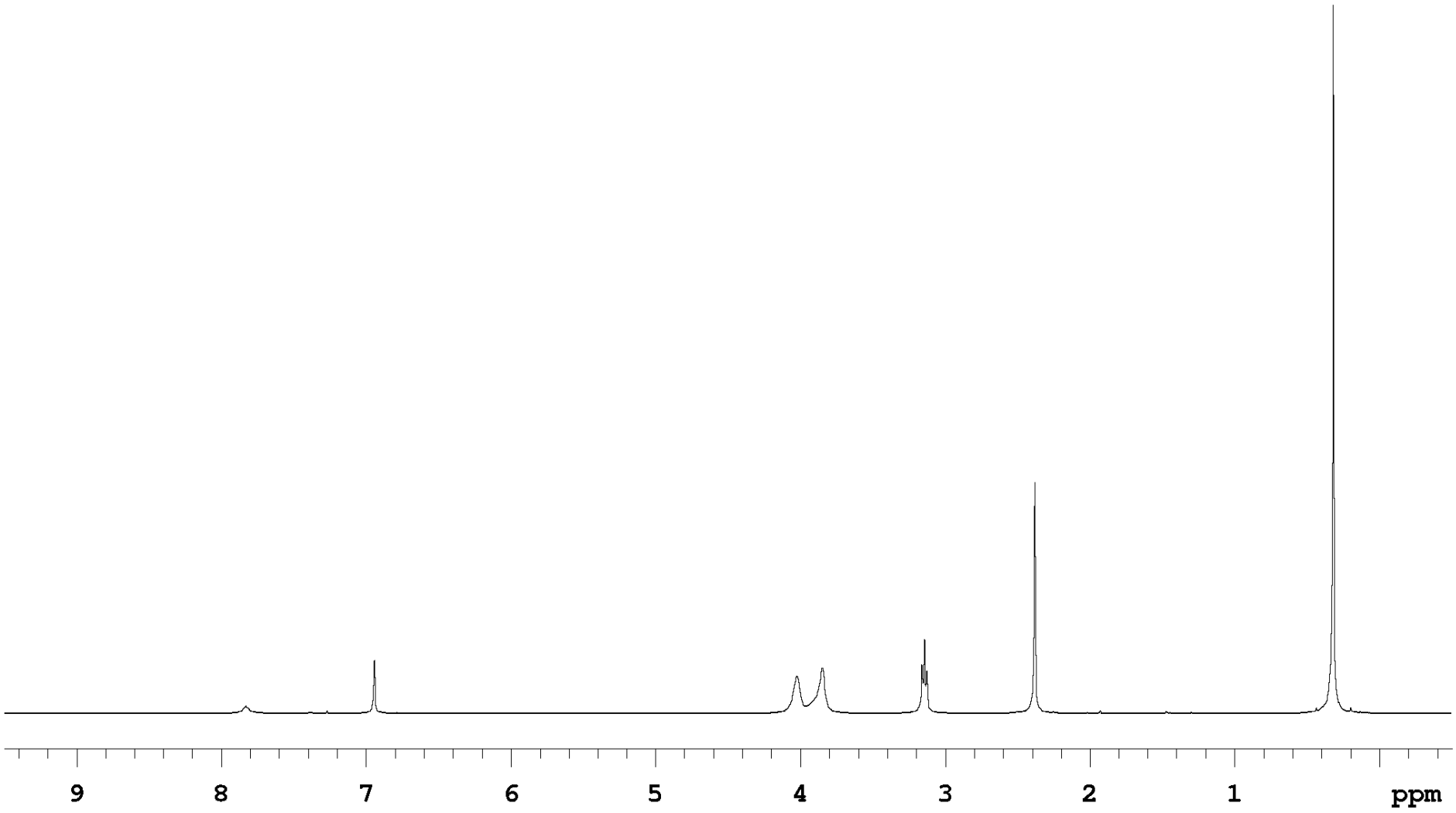

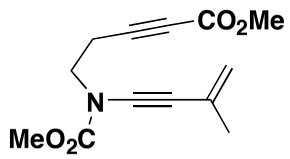

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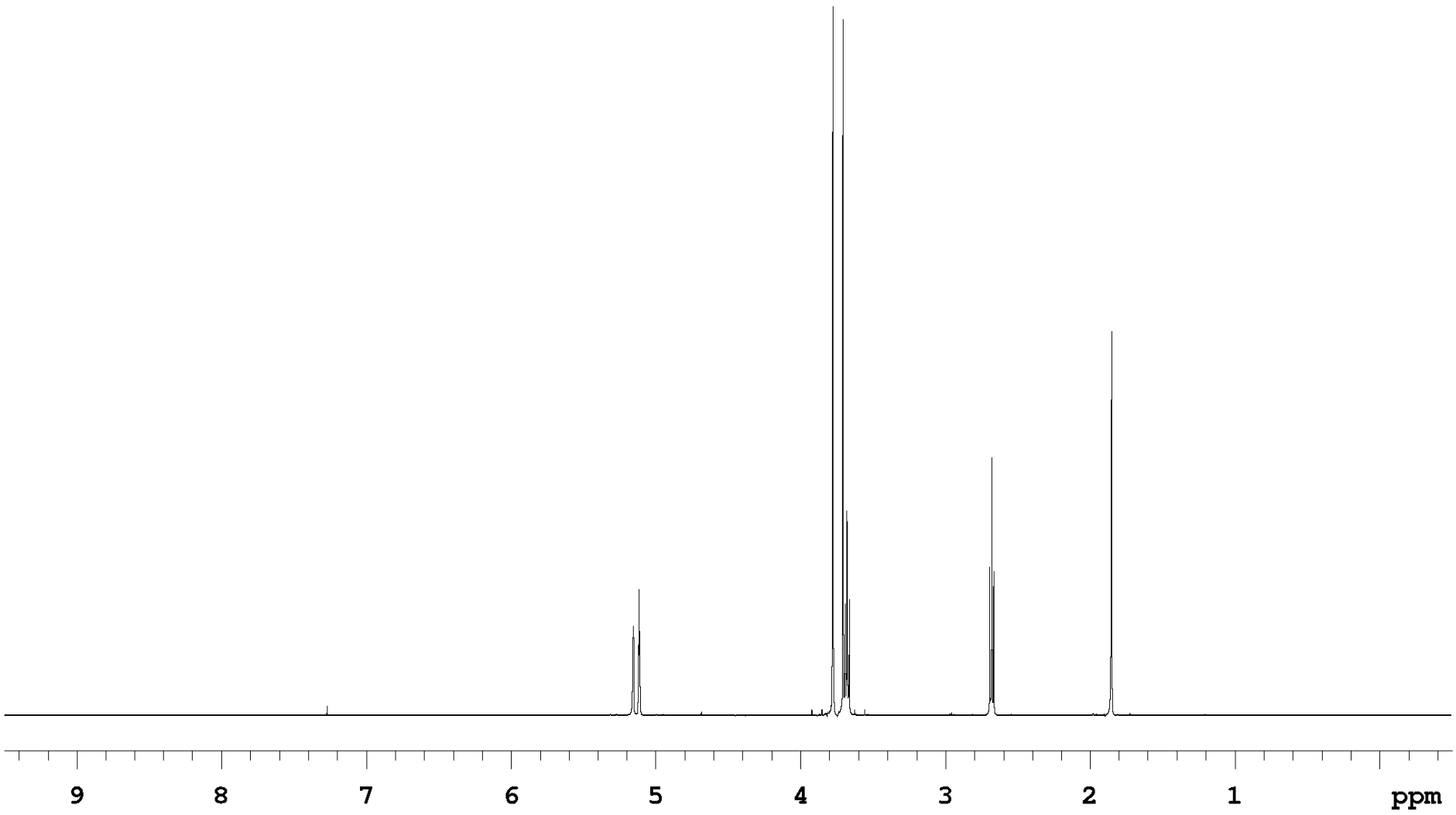

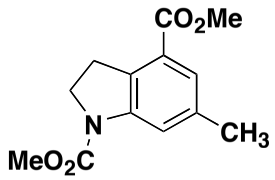

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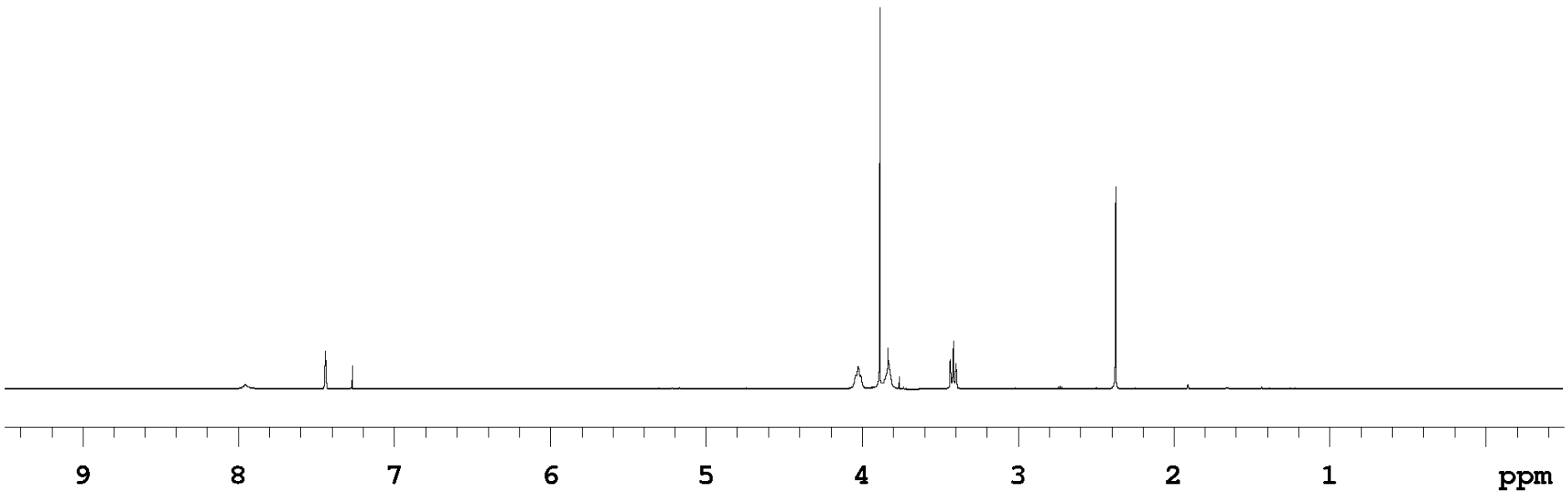

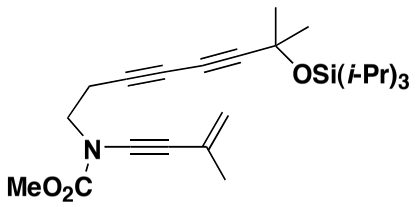

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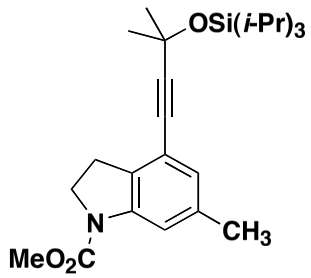

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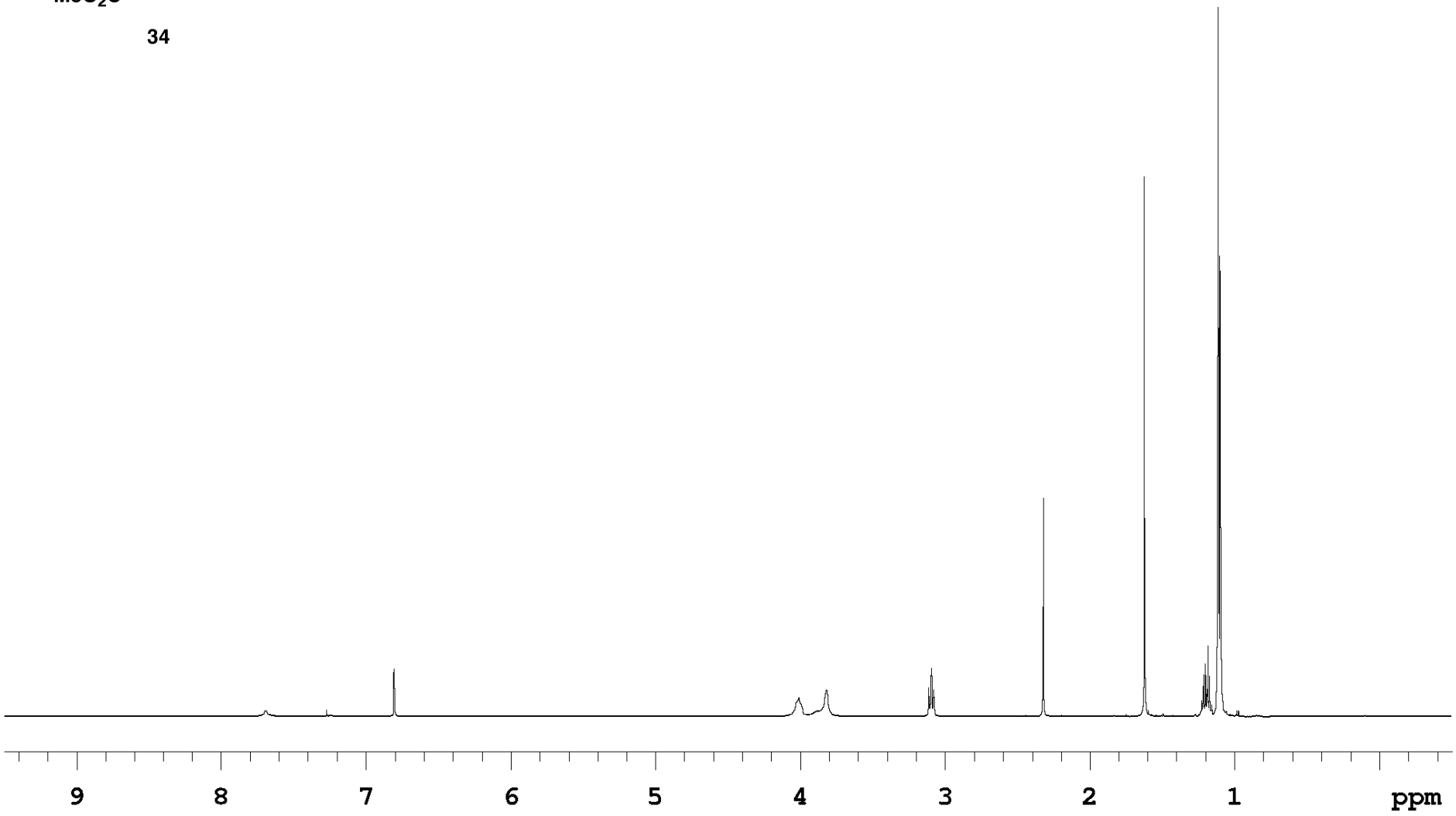

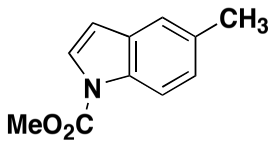

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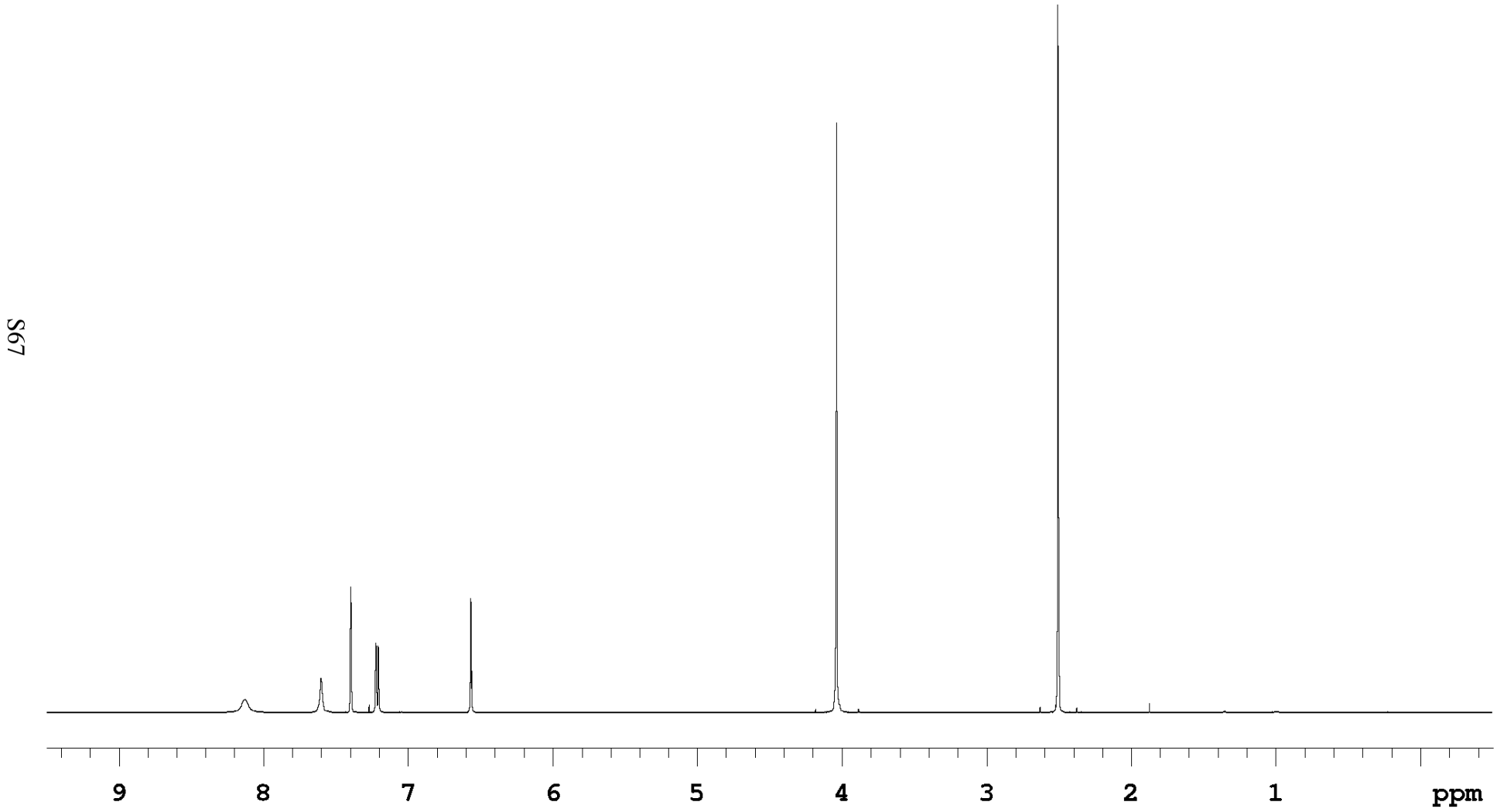

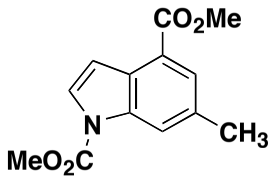

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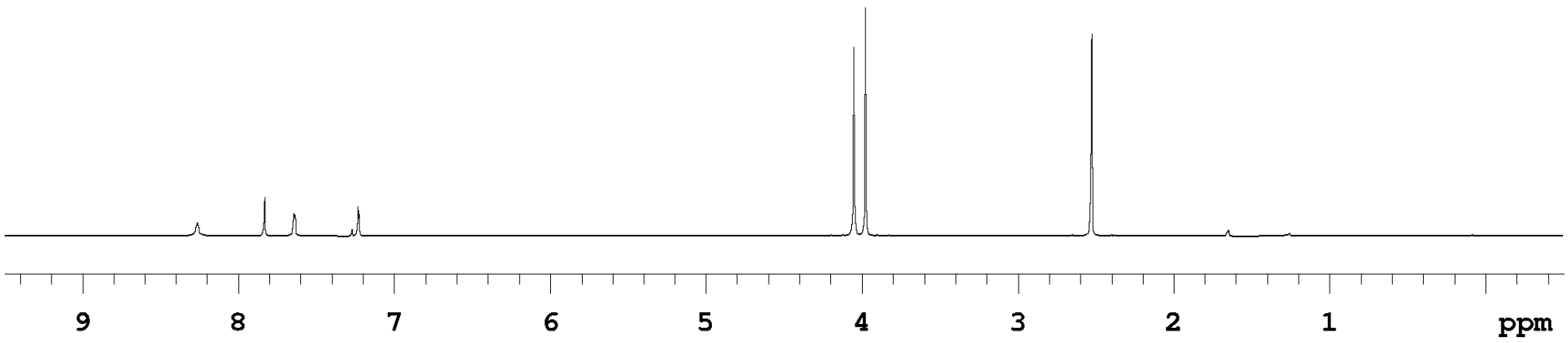

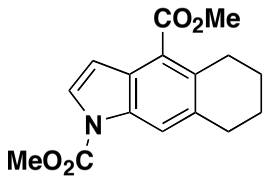

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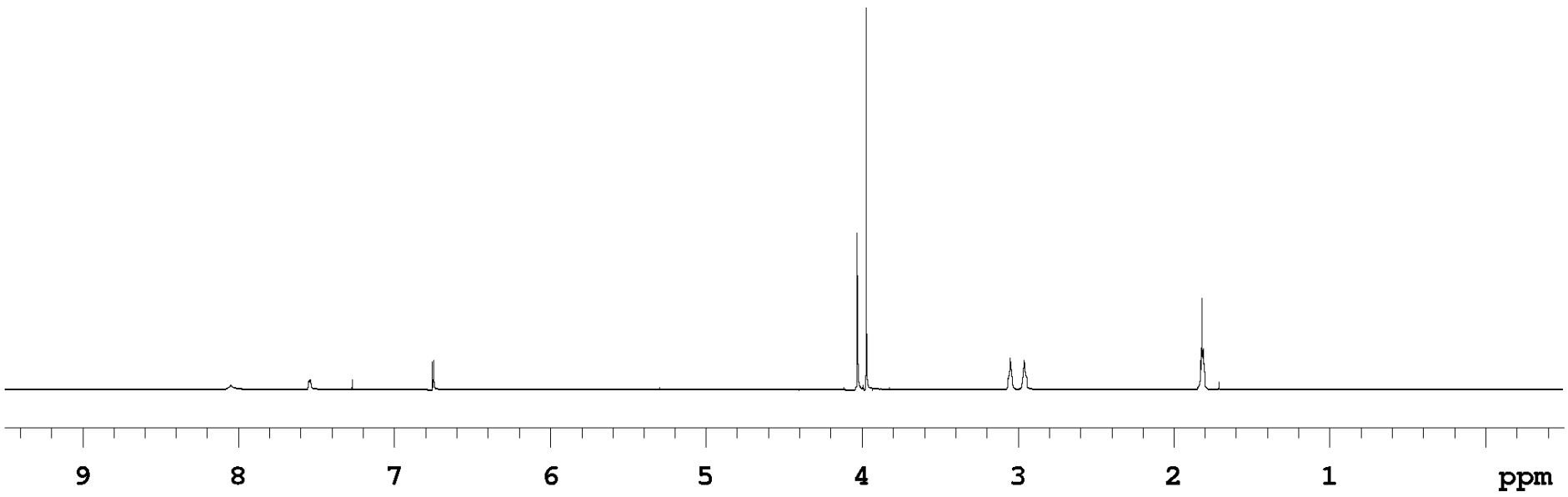

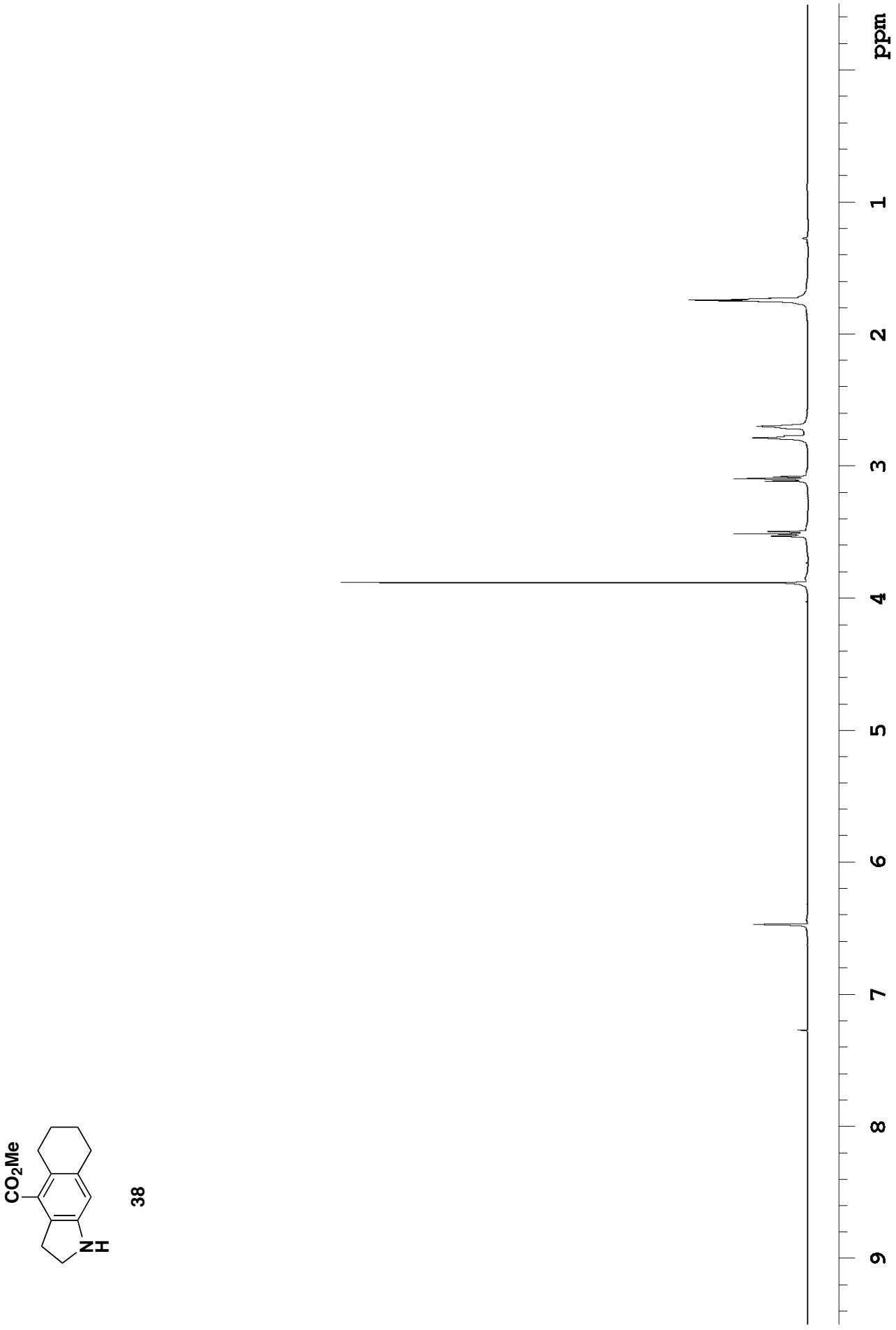
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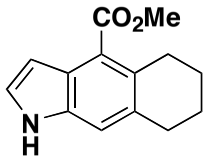

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