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Supporting Information

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Total Synthesis of Macbecin I

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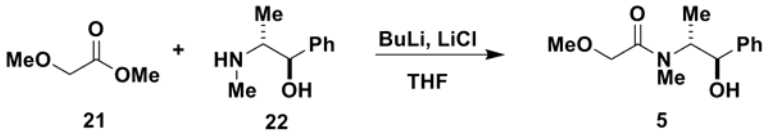
SUPPORTING INFORMATION:

General. All reactions were conducted in flame-dried glassware under nitrogen using anhydrous solvents. Toluene was dried by distillation over sodium and benzophenone. Diisopropylamine was dried by distillation over NaOH and triethylamine was distilled over CaH_2. Methylene chloride, tetrahydrofuran, benzene, and diethyl ether were used after passing through activated alumina columns. All other commercially available reagents were used as received.

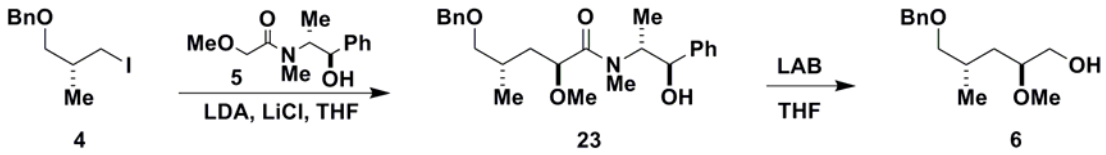
^{1}H NMR data were recorded at 500 MHz or 400 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR data were recorded at 126 MHz or 100 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument. ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.0 ppm). ^{13}C data for compound **1** was obtained on a Varian Inova-800. Infrared spectra were recorded using a Thermo Electron Nicolet 6700 FT-IR Spectrometer. Low resolution mass spectrometry was performed on a Waters Micromass® ZQ™ instrument using electrospray ionization (EI) or chemical ionization (CI). Optical rotations were measured on Perkin Elmer Model 341 polarimeter using a 1 mL capacity micro cell with a 10 cm path length. Chromatographic purifications were performed using 60Å, 35-75μm particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Semi-preparative and analytical HPLC normal phase separations were performed using an HPLC system composed of two Dynamax SD-1 pumps, a Rheodyne injector and a Dynamax UV-1 absorbance detector.



Synthesis of (*R*,*R*)-α-methoxy-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide, 5: A solution of *n*-butyllithium in hexanes (2.5 M, 12.1 mL, 30.3 mmol) was added to an ice-cooled suspension of lithium chloride (7.7 g, 181 mmol) and (−)-pseudoephedrine **22** (10 g, 60.5 mmol) in tetrahydrofuran (400 mL), and the suspension was stirred at 0 °C for 30 min. Methyl methoxyacetate **21** (12.0 mL, 121 mmol) was added via syringe over 5 min, and the mixture was warmed to 23 °C and stirred at that temperature for 3 h. A solution of 0.5 N NaOH (200 mL) was added, and the biphasic mixture was stirred at 23 °C for 1 h. Volatile organic solvents were removed under reduced pressure, and the resulting aqueous residue was extracted with five 50-mL portions of 10% methanol-dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the product by flash column chromatography eluting with methanol-dichloromethane (8 %) afforded amide **5** as a colorless oil which slowly solidified. The solid was subsequently recrystallized from hot toluene furnishing pure crystalline amide **5** as a 1.3:1 mixture of rotamers (12.6 g, 53.1 mmol, 88%).

Data for (*R*,*R*)-α-methoxy-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide, 5: $[\alpha]_{589}^{20}$ −98.7 ° (*c* = 1.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.24 (m, 10H), 4.62 (app. t, *J* = 7.6 Hz, 1H), 4.51 (dd, *J* = 9.1, 4.7 Hz, 1H), 4.46-4.38 (m, 1H), 4.22-4.16 (m, 2H), 4.10-3.96 (m, 4H), 3.45 (s, 3H), 3.37 (s, 3H), 3.19 (d, *J* = 4.4 Hz, 1H), 2.93 (s, 3H), 2.80 (s, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 141.6, 128.7, 128.4, 128.2, 127.7, 126.7, 126.3, 76.1, 75.2, 72.3, 71.7, 59.1, 58.9, 57.8, 26.7, 15.6, 14.2; IR (thin film, NaCl) 3392, 2984, 2934, 1646, 1452, 1408, 1317, 1199,

1109, 1050, 1024, 761 cm^{-1}; LRMS (EI, Na) calcd for $C_{13}H_{19}NO_3Na$, 260.14 *m/z* $(M + Na)^+$; observed, 260.27 $(M + Na)^+$ *m/z*.

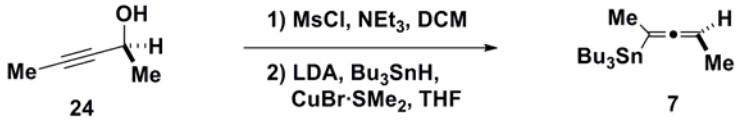


Synthesis of (2*S*,4*S*)-5-(benzyloxy)-2-methoxy-4-methylpentan-1-ol, 6. A 250 mL flask containing lithium chloride (6.5 g, 155 mmol) was flame-dried and to it was added diisopropylamine (7.38 mL, 52.6 mmol) and THF (110 mL). The suspension was cooled to −78 °C, and to it was added *n*-butyllithium in hexanes (2.5 M, 19.5 mL, 48.8 mmol). The resulting solution was warmed to 0 °C briefly and then was cooled to –78 °C. Amide **5** (5.8 g, 24.4 mmol) was added, and the solution was stirred at –78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min. The mixture was cooled to 0 °C, and iodide **4** (4.00 g, 13.78 mmol) was added to the reaction via syringe as a solution in 10 mL of THF. The reaction was stirred for 24 hours at 0 °C and was quenched with half-saturated NH_4Cl solution (100 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL), and the organic layer was then dried over Na_2SO_4. The solution was filtered through a pad of silica gel, rinsing with ethyl acetate (200 mL). All volatiles were removed *in vacuo*, and the resulting oil **23** was used in the following reaction.

A flame-dried 250 mL flask was charged with 80 mL of THF and 8.1 mL of diisopropylamine (57.8 mmol). This solution was cooled to –78 °C and 21.5 mL of *n*-butyllithium (2.5 M in hexanes, 53.7 mmol) was added dropwise via syringe. The resulting solution was warmed to 0 °C and stirred for 10 min before the addition of borane-ammonia complex (90%, 1.89 g, 55.12 mmol). The resulting suspension was stirred at 0 °C for 15 min

and at 23 °C for 15 min. The resulting white suspension was cooled to 0 °C and the crude amide **23** was added via syringe as a solution in 10 mL of THF. The solution was allowed to warm to 23 °C, and was stirred for 2 h. The reaction was slowly quenched with NH_4Cl (aq., sat) (50 mL) and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with $NaHCO_3$ (aq., sat) (1 × 100 mL) and brine (1 × 100 mL) before being dried over Na_2SO_4. The solution was filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (30% ethyl acetate-hexanes) affording the colorless oil **6** (2.29 g, 9.65 mmol, 70% over 2 steps) as a 9:1 mixture of diastereomers.

Data for (2*S*,4*S*)-5-(benzyloxy)-2-methoxy-4-methylpentan-1-ol, 6. $[\alpha]_{589}^{20}$ +6.19 ° (*c* 0.63, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 4.50 (app. s, 2H), 3.71 (ddd, *J* = 11.3, 6.1, 3.6 Hz, 1H), 3.48 (ddd, *J* = 11.6, 5.8, 5.8 Hz, 1H), 3.41-3.37 (m, 1H), 3.39 (s, 3H), 3.34-3.27 (m, 2H), 1.98-1.91 (m, 2H), 1.74 (ddd, *J* = 14.2, 7.4, 5.5 Hz, 1H), 1.22 (ddd, *J* = 13.9, 8.1, 5.2 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 128.3, 127.5, 127.4, 79.5, 75.9, 73.0, 64.0, 57.0, 35.0, 30.0, 17.5; IR (thin film, NaCl) 3447, 2930, 1457, 1363, 1204, 1099, 737, 698, 668 cm^{-1}; LRMS (EI, Na) calcd for $C_{14}H_{22}O_3Na$, 261.16 *m/z* $(M + Na)^+$; observed, 261.18 $(M + Na)^+$ *m/z*.

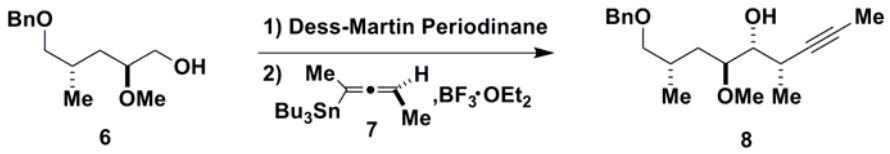


Synthesis of *M*-(-)-2-(Tributylstannyl)-2,3-pentadiene, 7 . To a mixture of 3-pentyn-2-ol **24** (2.00 g, 23.77 mmol) and NEt_3 (6.6 mL, 47.54 mmol) in 120 mL of CH_2Cl_2, was added methanesulfonyl chloride (2.78 mL, 35.65 mmol) at 0 °C. The resulting mixture was stirred at

0 °C for 1 h, then quenched with $NaHCO_3$ (aq., sat) (100 mL), and extracted with ether (3 × 50 mL). The ether layer was washed with brine (1 × 200 mL) and dried over Na_2SO_4. Concentration yielded crude mesylate, which was dried *in vacuo* and directly used for the next reaction without further purification.

To a flame-dried flask charged with diisopropylamine (3.66 mL, 26.2 mmol) and THF (150 mL) was added *n*-BuLi (2.5 M in hexanes, 9.5 mL, 23.77 mmol) at 0°C. After 30 min, tributyltin hydride (5.98 mL, 22.6 mmol) was added dropwise, and the mixture was stirred an additional 30 min. The yellow solution was then cooled to −78°C and $CuBr{\cdot}SMe_2$ (4.64 g, 22.6 mmol) was added portion-wise. Once addition was complete, the dark solution was stirred an additional 30 min before the mesylate was added. After 10 min, the solution was poured into a rapidly stirring solution of 500 mL of 9:1 NH_4Cl/NH_4OH solution and 300 mL of ether. Once the ether layer clarified, it was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was purified by chromatography using basic alumina and eluting with hexanes. The recovered stannane **7** (6.05 g, 71% over 2 steps) was obtained as a clear and colorless oil, and was of sufficient purity for use in the subsequent propargylation.

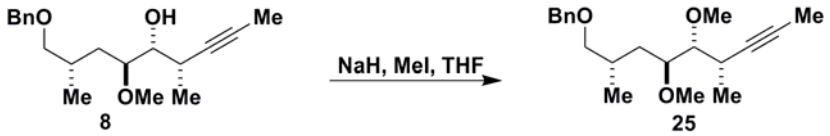
Data for *M*-(-)-2-(Tributylstannyl)-2,3-pentadiene, 7: $[\alpha]_{589}^{20}$ −50.0 ° (*c* = 1.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59-4.51 (m, 1H), 1.81 (app. d, *J* = 3.1 Hz, 3H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.59-1.45 (m, 6H), 1.39-1.27 (m, 6H), 1.04-0.87 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 87.4, 75.5, 29.2, 27.6, 19.2, 14.3, 14.0, 9.8; IR (thin film, NaCl) 2957, 2926, 2872, 2855, 1943, 1733, 1465, 1457, 1377, 1071, 972 cm^{-1}; LRMS (EI, Na) calcd for $C_{17}H_{34}SnH$, 359.17 *m/z* $(M + H)^+$; observed, 359.24 $(M + H)^+$ *m/z*.



Synthesis of (2*S*,4*S*,5*R*,6*S*)-1-benzyloxy-4-methoxy-2,6-dimethylnon-7-yn-5-ol, 8: To a stirring solution of **6** (110 mg, 0.461 mmol) in dichloromethane (1.0 mL, reagent grade) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (347 mg, 0.629 mmol) at room temperature. After 1 h of stirring, the reaction was diluted with a solution of 20 % EtOAc/ hexanes (10 mL) and most of the solvent was removed. The residue was dissolved in 10 mL of EtOAc/ hexanes and washed with a 1:1 mixture of 10 % $Na_2S_2O_3$ and $NaHCO_3$ (sat) solution until a clear organic layer was obtained. The organic layer was then washed with brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The solution was then filtered and its solvent was removed *in vacuo* affording the corresponding aldehyde (107 mg, 0.454 mmol) as a yellow oil. The oil was further dried via azeotropic removal of water (concentrated from anhydrous benzene (3 × 3 mL)). The aldehyde was then used in the subsequent step without further purification.

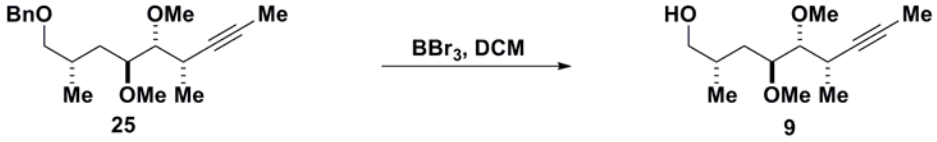
To a flame-dried 10 mL flask containing stannane **7** (324 mg, 0.908 mmol) in 1.0 mL of dichloromethane at –78 ^oC was added the aldehyde from the previous reaction (107 mg, 0.454 mmol) in 1.0 mL of dichloromethane. $BF_3{\cdot}OEt_2$ (57 μL, 0.91 mmol) was added slowly via syringe and the solution was stirred at –78 ^oC for 30 min. To the solution was added $NaHCO_3$ (aq., sat) (5 mL) and the mixture was warmed to rt. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and the volatiles were removed *in vacuo*. The crude product was purified using flash column chromatography (10% ethyl acetate-hexanes) affording a single diastereomer of homopropargylic alcohol **8** (70 mg, 0.23 mmol, 50 % over 2 steps, d.s. = 4:1).

(2*S*,4*S*,5*R*,6*S*)-1-benzyloxy-4-methoxy-2,6-dimethylnon-7-yn-5-ol, 8: $[\alpha]_{589}^{20}$ −29.4 ^{o} (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.53 (A of AB, *J* = 12.6 Hz, 1H), 4.52 (B of AB, *J* = 12.6 Hz, 1H), 3.72-3.68, (m, 1H), 3.59 (ddd, *J* = 10.3, 2.6, 2.6 Hz, 1H), 3.39 (s, 3H), 3.35 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.28 (dd, *J* = 9.0, 7.1 Hz, 1H), 2.43-2.35 (m, 1H), 2.31 (d, *J* = 1.6 Hz, 1H), 2.08-2.00 (m, 1H), 1.78 (d, *J* = 2.3 Hz, 3H), 1.66 (ddd, *J* = 13.9, 10.3, 3.2 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.25-1.20 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 128.3, 127.6, 127.4, 80.1, 79.9, 77.8, 76.5, 73.5, 73.0, 57.1, 31.5, 29.8, 28.8, 18.4, 16.7, 3.4; IR (thin film, NaCl) 3447, 2919, 1496, 1457, 1363, 1260, 1092, 1029, 928, 802, 736, 698 cm^{-1}; LRMS (EI, Na) calcd for $C_{19}H_{28}O_3Na$, 327.20 *m/z* (M + Na)$^{+}$; observed, 327.30 (M + Na)$^{+}$ *m/z*.



Synthesis of (2*S*,4*S*,5*R*,6*S*)-1-benzyloxy-4,5-dimethoxy-2,6-dimethyl-7-nonyne, 25: To a flame-dried 10 mL flask containing a suspension of NaH (60%, 53 mg, 1.3 mmol) in THF (1.0 mL) was added homopropargylic alcohol **8** (200 mg, 0.66 mmol) via syringe as a solution in THF (1.0 mL) at 0 ^{o}C. After 30 min, methyl iodide (164 μL, 2.62 mmol) was added via syringe and the solution was warmed to 23 ^{o}C and held at this temperature for 1 h. The solution was quenched slowly with NH_4Cl (aq., sat) (5 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the volatiles were removed *in vacuo*. The crude product was purified using flash column chromatography (10% ethyl acetate-hexanes) affording the corresponding methyl ether **25** (205 mg, 0.64 mmol, 98 %) as a colorless oil.

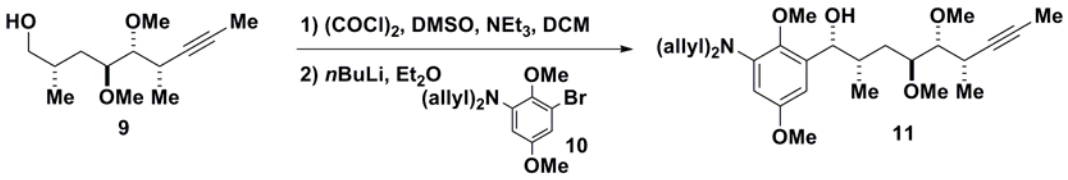
(2*S*,4*S*,5*R*,6*S*)-1-benzyloxy-4,5-dimethoxy-2,6-dimethyl-7-nonyne, 25: $[\alpha]_{589}^{20}$ −5.45 ^{o} (*c* 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.51 (A of AB, *J* = 12.3 Hz, 1H), 4.50 (B of AB, *J* = 12.3 Hz, 1H), 3.64 (ddd, *J* = 10.0, 2.3, 2.3 Hz, 1H), 3.51 (s, 3H), 3.41-3.38 (m, 1H), 3.39 (s, 3H), 3.27-3.23 (m, 2H), 2.44-2.37, (m, 1H), 2.08-2.00 (m, 1H), 1.78 (d, *J* = 2.6 Hz, 3H), 1.67 (ddd, *J* = 14.2, 10.3, 3.6 Hz, 1H), 1.25-1.19 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 128.3, 127.5, 127.3, 84.3, 80.9, 80.8, 77.2, 76.5, 72.9, 60.6, 57.2, 33.0, 30.1, 28.6, 18.2, 16.8, 3.5; IR (thin film, NaCl) 2931, 1454, 1363, 1196, 1099, 1028, 735, 698 cm^{-1}; LRMS (EI, Na) calcd for $C_{20}H_{30}O_3Na$, 341.22 *m/z* $(M + Na)^+$; observed, 341.35 $(M + Na)^+$ *m/z*.



Synthesis of (2*S*,4*S*,5*R*,6*S*)-4,5-dimethoxy-2,6-dimethylnon-7-yn-1-ol, 9: To a solution of **25** (1.4 g, 4.4 mmol) in dichloromethane (50 ml) at –78 ^{o}C was added fresh BBr_3 (5.2 mL of a 1M solution in CH_2Cl_2). The solution was left to stir at –78 ^{o}C for 30 min before quenching with $NaHCO_3$ (aq., sat) (10 ml). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and removal of solvent *in vacuo*, the crude mixture was purified by flash column chromatography (50% ethyl actetate-hexanes) to provide pure alcohol **9** (744 mg, 3.3 mmol, 74 % yield).

(2S,4S,5R,6S)-4,5-dimethoxy-2,6-dimethylnon-7-yn-1-ol, 9: $[\alpha]_{589}^{20}$ −14.1^{o} (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (ddd, *J* = 10.1, 1.8, 1.8 Hz, 1H), 3.56-3.49 (m, 1H), 3.51 (s, 3H), 3.47-3.40 (m, 1H), 3.42 (s, 3H), 3.26 (dd, *J* = 8.6, 2.0 Hz, 1H), 2.45 (app t, *J* = 6.0 Hz, 1H), 2.42-2.34 (m, 1H), 1.82 (ddd, *J* = 12.9, 12.9, 6.3 Hz, 1H), 1.78 (d, *J* = 2.5 Hz,

3H), 1.63 (ddd, *J* = 14.9, 10.1, 6.3 Hz, 1H), 1.36 (ddd, *J* = 14.6, 7.0, 1.8 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.7, 82.4, 80.5, 78.0, 68.6, 60.6, 56.8, 33.8, 33.2, 28.8, 18.4, 17.7, 3.5; IR (thin film, NaCl) 3420, 2933, 1457, 1347, 1195, 1095, 1043 cm^{-1}; LRMS (EI, Na) calcd for $C_{13}H_{24}O_3Na$, 251.17 *m/z* $(M + Na)^+$; observed, 251.00 $(M + Na)^+$ *m/z*.



Synthesis of (1*R*,2*S*,4*S*,5*R*,6*S*)-1-(3-(diallylamino)-2,5-dimethoxyphenyl)-4,5-dimethoxy-2,6-dimethylnon-7-yn-1-ol, 11: To a solution of DMSO (694 μl, 9.78 mmol) in dichloromethane (14ml) at –78 ^{o}C was added oxalyl chloride (570 μl, 6.52 mmol) slowly over 5 min. After 30 min at –78 ^{o}C, alcohol **9** (744 mg, 3.26 mmol) was added as a solution in dichloromethane (2 mL) slowly over 10 min. The solution slowly turned to a white slurry over 30 min at –78 ^{o}C, after which time NEt_3 (2.7 ml, 19.6 mmol) was added slowly and the solution was allowed to warm to rt over 1 h. The solution was washed with 1N $KHSO_4$ (10 ml), $NaHCO_3$ (aq., sat) (10 ml), and brine (10 ml). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The aldehyde was immediately used crude in the following reaction.

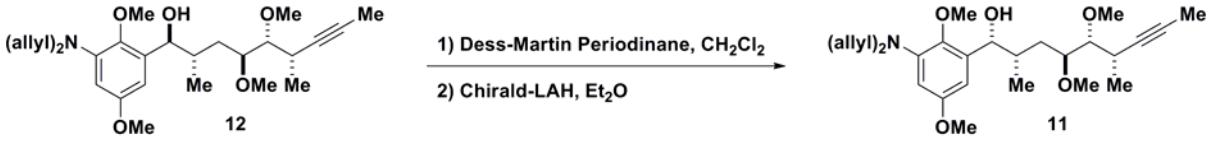
To a flame-dried 250 ml flask charged with aryl bromide **10** (2.6 g, 9.78 mmol) in diethyl ether (90 ml) at –78 ^{o}C, was added *n*BuLi (2.0M solution in hexanes, 4.4 ml, 8.8 mmol). The solution was allowed to warm to rt over 30 min and stirred at rt for 1h. The bright yellow solution was then recooled to –78 ^{o}C, and the previously made aldehyde was added as

a solution in diethyl ether (10 mL) slowly over the course of 10 min. After 1h at –78 °C the solution was quenched with $NaHCO_3$ (aq., sat) (25 ml), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (30% ethyl acetate-hexanes) to provide a mixture of diastereomers **11** and **12** (1.2 g, 2.61 mmol, 81% yield, d.r. = 2:1). The diastereomers could then be easily separated by flash column chromatography (25% ethyl acetate-hexanes) to provide pure desired diastereomer **11**, in addition to undesired diastereomer **12**.

(1*R*,2*S*,4*S*,5*R*,6*S*)-1-(3-(diallylamino)-2,5-dimethoxyphenyl)-4,5-dimethoxy-2,6-dimethylnon-7-yn-1-ol, 11: $[\alpha]_{589}^{20}$ +4.8 ° (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 2.8 Hz, 1H), 5.78 (dddd, *J* = 16.7, 10.4, 6.3, 6.3 Hz, 2H), 5.18-5.09 (m, 4H), 4.88 (app t, *J* = 4.5 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.76-3.72 (m, 4H), 3.49 (s, 3H), 3.42 (s, 3H), 3.26 (dd, *J* = 8.2, 2.2 Hz, 1H), 2.86 (d, *J* = 4.7 Hz, 1H), 2.47-2.39 (m, 1H), 2.13-2.05 (m, 1H), 1.79 (d, *J* = 2.5 Hz, 3H), 1.65 (ddd, *J* = 16.1, 9.8, 6.3 Hz, 1H), 1.46 (ddd, *J* = 14.5, 8.2, 1.6 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 143.9, 143.7, 137.2, 135.0, 117.3, 106.9, 104.4, 84.1, 82.2, 80.8, 77.8, 77.2, 72.6, 60.4, 59.1, 56.9, 55.5, 53.8, 36.6, 33.2, 28.6, 18.2, 14.5, 3.4; IR (thin film, NaCl) 3444, 2928, 1597, 1469, 1195, 1172, 1094, 1006, 919 cm^{-1}; LRMS (EI, Na) calcd for $C_{27}H_{41}NO_5Na$, 482.30 *m/z* $(M + Na)^+$; observed, 482.53 $(M + Na)^+$ *m/z*.

Data for isolated undesired diastereomer: (1*S*,2*S*,4*S*,5*R*,6*S*)-1-(3-(diallylamino)-2,5-dimethoxyphenyl)-4,5-dimethoxy-2,6-dimethylnon-7-yn-1-ol, 12: $[\alpha]_{589}^{20}$ −29.7 ° (*c* 1.64, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 2.8 Hz, 1H), 6.39 (d, *J* = 2.8 Hz, 1H), 5.83-5.74 (m, 2H), 5.19-5.09 (m, 4H), 4.61 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.78-3.71 (m, 4H), 3.79

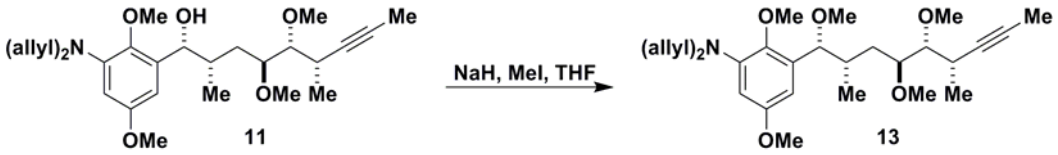
(s, 3H), 3.76 (s, 3H), 3.68 (ddd, *J* = 10.4, 2,2, 2.2 Hz, 1H), 3.52 (s, 3H), 3.43 (s, 3H), 3.28 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.14 (d, *J* = 5.0 Hz, 1H), 2.49-2.41 (m, 1H), 2.12 (ddd, *J* = 14.5, 10.4, 3.8 Hz, 1H), 2.03-1.96 (m, 1H), 1.78 (d, *J* = 2.5 Hz, 3H), 1.38 (ddd, *J* = 14.5, 7.9, 1.9 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 144.7, 143.9, 137.8, 135.0, 117.2, 107.0, 104.3, 84.0, 81.9, 80.9, 77.7, 77.2, 74.8, 60.5, 59.6, 57.0, 55.4, 53.9, 37.6, 33.2, 28.6, 18.1, 17.3, 3.5; IR (thin film, NaCl) 3447, 2930, 1653, 1597, 1473, 1195, 1102, 919 cm^{-1}; LRMS (EI, Na) calcd for $C_{27}H_{41}NO_5Na$, 482.30 *m/z* $(M + Na)^+$; observed, 482.53 $(M + Na)^+$ *m/z*.



Recycling of undesired diastereomer, 12, to desired diastereomer, 11: To a stirring solution of **12** (37 mg, 0.10 mmol) in dichloromethane (0.5 mL, reagent grade) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (130 mg, 0.30 mmol) at 0 ^{o}C. After 5 h of stirring, the reaction was filtered through a short pad of silica, eluting with 20% ethyl acetate-hexanes until all of the benzylic ketone eluted from the silica. The solution was then concentrated *in vacuo* affording the corresponding ketone as a yellow oil.

To a flame-dried flask containing the ketone from the previous reaction in Et_2O at rt was carefully added lithium aluminum hydride (1.0 M in Et_2O, 153 μL, 0.15 mmol). The solution was stirred at rt × 20 min before cooling to 0 ^{o}C and carefully quenching with water (0.3 ml). The entire mixture was loaded on a silica-gel column and was eluted with 30% ethyl acetate-hexanes to provide **11** and **12** as a mixture of diastereomers (28 mg, 76% yield, 1:1 d.r.). The diastereomers could then be easily separated by flash column chromatography (25%

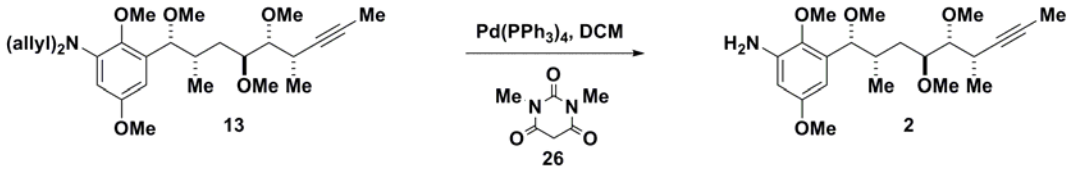
ethyl acetate-hexanes) to provide pure desired diastereomer **11**, in addition to undesired diastereomer **12**.



Synthesis of *N*,*N*-diallyl-2,5-dimethoxy-3-((1*R*,2*S*,4*S*,5*R*,6*S*)-1,4,5-trimethoxy-2,6-dimethylnon-7-ynyl)aniline, 13: To a flame-dried 10 mL flask containing a suspension of NaH (60%, 230 mg, 5.7 mmol) in THF (1.8 mL) was added benzylic alcohol **11** (262 mg, 0.57 mmol) via syringe as a solution in THF (1.0 mL) at 0 ^{o}C. After 30 min, methyl iodide (800 μL, 11.4 mmol) was added via syringe and the solution was warmed to rt and stirred at this temperature for 36 h. The solution was quenched slowly with NH_4Cl (aq., sat) (5 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the volatiles were removed *in vacuo*. The crude product was purified using flash column chromatography (20 % ethyl acetate-hexanes) affording the pure methyl ether **13** (239 mg, 0.51 mmol, 89% yield).

***N*,*N*-diallyl-2,5-dimethoxy-3-((1*R*,2*S*,4*S*,5*R*,6*S*)-1,4,5-trimethoxy-2,6-dimethylnon-7-ynyl)aniline, 13:** $[\alpha]_{589}^{20}$ +35.9 ^{o} (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (d, *J* = 3.1 Hz, 1H), 6.38 (d, *J* = 3.1 Hz, 1H), 5.84-5.75 (m, 2H), 5.19-5.09 (m, 4H), 4.40 (d, *J* = 5.0 Hz, 1H), 3.81-3.70 (m, 4H), 3.76 (s, 3H), 3.75 (s, 3H), 3.59 (ddd, *J* = 10.1, 2.8, 2.8 Hz, 1H), 3.46 (s, 3H), 3.34 (s, 3H), 3.24 (s, 3H), 3.20 (dd, *J* = 8.2, 3.1 Hz, 1H), 2.49-2.41 (m, 1H), 2.03-1.94 (m, 1H), 1.76 (d, *J* = 2.5 Hz, 3H), 1.64 (ddd, *J* = 13.9, 9.8, 3.5 Hz, 1H), 1.41 (ddd, *J* = 14.2, 10.4, 2.5 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 145.1, 143.8, 135.3, 135.1, 117.2, 106.7, 103.7, 84.5, 82.4, 81.1, 80.8,

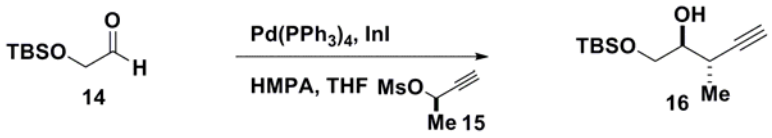
77.4, 77.2, 60.4, 59.0, 57.3, 57.0, 55.4, 53.7, 35.6, 33.2, 28.3, 17.9, 14.0, 3.5; IR (thin film, NaCl) 2931, 2821, 1598, 1475, 1351, 1196, 1172, 1100, 1059, 1008, 957, 920, 846 cm^{-1}; LRMS (EI, Na) calcd for $C_{28}H_{43}NO_5H$, 474.31 *m/z* $(M + H)^+$; observed, 474.60 $(M + H)^+$ *m/z*.



Synthesis of 2,5-dimethoxy-3-((1*R*,2*S*,4*S*,5*R*,6*S*)-1,4,5-trimethoxy-2,6-dimethylnon-7-ynyl)aniline, 2: To a stirring solution of *N*,*N*-diallyl aniline **13** (20 mg, 0.042 mmol) in dichloromethane (0.9 ml) was added *N*,*N*-dimethylbarbituric acid **26** (40 mg, 0.253 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.0084 mmol). After 3 h of heating at reflux, the reaction was cooled to rt and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (20 ml) and washed with Na_2CO_3 (aq., sat) (3 x 5 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification of the residue by flash column chromatography (35% ethyl acetate-hexanes) provided the pure desired aniline **2**(16 mg, 0.041 mmol, 98% yield) as a yellow foam.

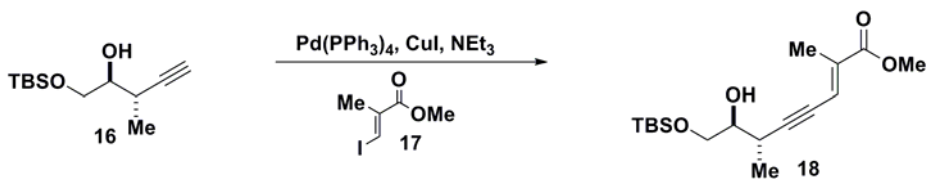
2,5-dimethoxy-3-((1*R*,2*S*,4*S*,5*R*,6*S*)-1,4,5-trimethoxy-2,6-dimethylnon-7-ynyl)aniline, 2: $[\alpha]_{589}^{20}$ +21.3 ^{o} (*c* 1.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, J = 2.8 Hz, 1H), 6.22 (d, J = 3.1 Hz, 1H), 4.34 (d, J = 4.7 Hz, 1H), 3.77 (br s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.58 (ddd, J = 10.1, 2.5, 2.5 Hz, 1H), 3.47 (s, 3H), 3.34 (s, 3H), 3.23 (s, 3H), 3.21 (dd, J = 8.0, 2.8 Hz, 1H), 2.50-2.39 (m, 1H), 2.07-1.96 (m, 1H), 1.75 (d, J = 2.5 Hz, 3H), 1.67 (ddd, J = 13.9, 10.1, 3.5 Hz, 1H), 1.43 (ddd, J = 14.2, 10.4, 2.5 Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 140.3, 140.0, 135.0, 101.6, 100.9, 84.5, 82.3, 81.1, 80.8, 77.5, 60.4, 59.8, 57.2, 57.0, 55.3, 35.5, 33.4, 28.3, 18.0, 13.8, 13.4; IR (thin

film, NaCl) 3447, 3355, 2933, 2826, 1616, 1457, 1352, 1239, 1196, 1169, 1156, 1098, 1046, 1002, 953, 837 cm^{-1}; LRMS (EI, Na) calcd for $C_{22}H_{35}NO_5Na$, 416.25 *m/z* $(M + Na)^+$; observed, 416.41 $(M + Na)^+$ *m/z*.



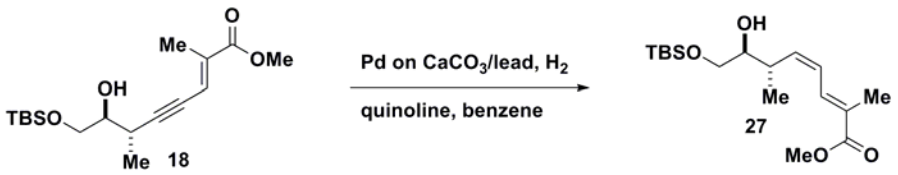
Synthesis of (2*S*,3*S*)-1-(tert-butyldimethylsilyloxy)-3-methylpent-4-yn-2-ol, 16: To a solution of aldehyde **14** (240 mg, 1.6 mmol) in THF (2.2 ml) and HMPA (1.6 ml) at 0 ^oC, was added $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) and InI (460 mg, 1.76 mmol). A solution of freshly prepared mesylate **15** (308 mg, 1.78 mmol) in THF (1.0 ml) was then added dropwise over 5 min. After stirring at 0 ^oC for 20 min, the solution was warmed to rt and stirred for 1 h. The mixture was then loaded on a large silica-gel column eluting with 10 % ethyl acetate-hexanes. Alkyne **16** (300 mg, 1.3 mmol, 82% yield) was initially isolated as a mixture of diastereomers (d.r. = 5:1); however, further purification by flash column chromatography (0-5% ethyl acetate-hexanes) afforded pure **16** as a single isomer that was isolated as a white solid.

(2*S*,3*S*)-1-(tert-butyldimethylsilyloxy)-3-methylpent-4-yn-2-ol, 16: $[\alpha]_{589}^{20}$ −13.8 ^{o} (*c* 1.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.68-3.60 (m, 2H), 3.56-3.50 (m, 1H), 2.74-2.66 (m, 1H), 2.36 (br s, 1H), 2.08 (d, *J* = 2.5 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.9, 73.8, 70.5, 64.8, 28.9, 25.8, 18.2, 17.0, -5.4; IR (thin film, NaCl) 3446, 3312, 2930, 2858, 1472, 1257, 1093, 838, 778, 633 cm^{-1}; LRMS (EI, Na) calcd for $C_{12}H_{24}O_2SiNa$, 251.15 *m/z* $(M + Na)^+$; observed, 251.07 $(M + Na)^+$ *m/z*.



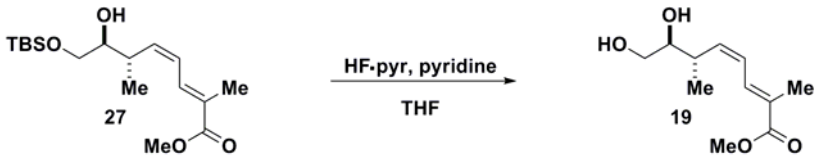
Synthesis of (6*S*,7*S*,*E*)-methyl 8-(tert-butyldimethylsilyloxy)-7-hydroxy-2,6-dimethyloct-2-en-4-ynoate, 18: To a solution of alkyne **16** (750 mg, 3.28 mmol) and vinyl iodide **17** (750 mg, 3.28 mmol) in NEt_3 (6.5 ml) was added $Pd(PPh_3)_4$ (190 mg, 0.17 mmol) and catalytic CuI (~10 mg) sequentially. The solution was allowed to stir at rt for 12h while monitoring by TLC. Additional CuI was added as necessary to reach the completion of the reaction. The NEt_3 was removed *in vacuo*, and the remaining residue was purified by flash column chromatography (10% ethyl acetate-hexanes) to afford pure product **18** (940 mg, 2.9 mmol, 88% yield) as a colorless oil.

(6*S*,7*S*,*E*)-methyl 8-(tert-butyldimethylsilyloxy)-7-hydroxy-2,6-dimethyloct-2-en-4-ynoate, 18: $[\alpha]_{589}^{20}$ −25.3 ^{o} (*c* 5.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (br s, 1H), 3.73 (s, 3H), 3.70-3.58 (m, 3H), 2.97-2.90 (m, 1H), 2.36 (d, *J* = 5.0 Hz, 1H), 2.02 (d, *J* = 1.3 Hz, 3H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 138.1, 120.0, 103.6, 79.5, 74.0, 64.9, 51.9, 30.4, 25.8, 18.2, 17.0, 15.2, -5.4; IR (thin film, NaCl) 3501, 2954, 1717, 1615, 1471, 1388, 1348, 1262, 1180, 1122, 1037, 1007, 979, 838, 747, 669 cm^{-1}; LRMS (EI, Na) calcd for $C_{17}H_{30}O_4SiH$, 327.19 *m/z* $(M + H)^+$; observed, 327.15 $(M + H)^+$ *m/z*.



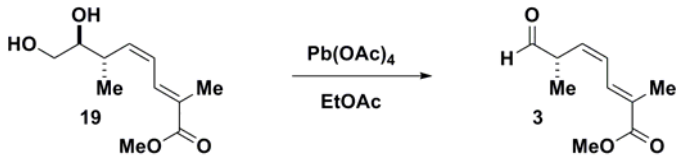
Synthesis of (2*E*,4*Z*,6*S*,7*S*)-methyl 8-(tert-butyldimethylsilyloxy)-7-hydroxy-2,6-dimethylocta-2,4-dienoate, 27: To a solution of alkyne **18** (270 mg, 0.82 mmol) in benzene (4.1 ml) at rt was added quinoline (1 ml) and Pd on $CaCO_3$ / poisoned with lead (174 mg). The atmosphere was purged with hydrogen gas and the reaction was stirred under a hydrogen balloon for 2 h. The reaction was carefully monitored by ^{1}HNMR to avoid any conversion to the inseparable corresponding alkane. Upon completion, the reaction was filtered through a plug of Celite to remove the catalyst, and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (10 % ethyl acetate-hexanes) provided **27** (251 mg, 0.76 mmol, 93% yield) as a colorless oil. The diene was further purified by HPLC (10% ethyl acetate-hexanes, isocratic) to provide characterization quality material.

(2*E*,4*Z*,6*S*,7*S*)-methyl 8-(tert-butyldimethylsilyloxy)-7-hydroxy-2,6-dimethylocta-2,4-dienoate, 27: $[\alpha]_{589}^{20}$ +17.7 ^{o} (*c* 0.48, $CHCl_3$); ^{1}H NMR 400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 11.9 Hz, 1H), 6.36 (app t, *J* = 11.4 Hz, 1H), 5.84 (app t, *J* = 10.6 Hz, 1H), 3.76 (s, 3H), 3.65 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.59-3.52 (m, 1H), 3.47 (dd, *J* = 9.6, 7.3 Hz, 1H), 2.97-2.85 (m, 1H), 2.43 (br s, 1H), 1.95 (d, *J* = 0.8 Hz, 3H), 1.07 (d, 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 141.1, 132.7, 127.6, 124.1, 75.0, 65.3, 51.8, 34.9, 25.8, 18.2, 17.4, 12.5, -5.4; IR (thin film, NaCl) 3501, 2954, 2929, 2857, 1712, 1633, 1463, 1436, 1254, 1108, 1005, 837, 778, 747 cm^{-1}; LRMS (EI, Na) calcd for $C_{17}H_{32}O_4SiNa$, 351.21 *m/z* $(M + Na)^+$; observed, 351.20 $(M + Na)^+$ *m/z*.



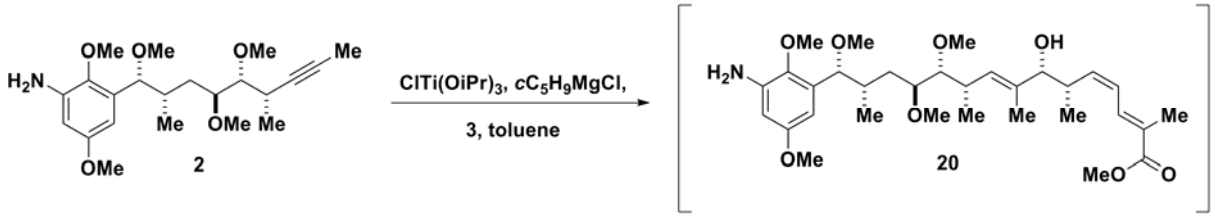
Synthesis of (2*E*,4*Z*,6*S*,7*S*)-methyl 7,8-dihydroxy-2,6-dimethylocta-2,4-dienoate, 19: To a solution of diene **27** (150 mg, 0.45 mmol) in THF (1.5 ml) and pyridine (450 μl), was added HF·pyr (300 μl) at rt. The solution was allowed to stir for 30 min before adding $NaHCO_3$ (aq., sat) (1 ml). The entire mixture was loaded on a large column eluting with 65% ethyl aceate-hexanes to provide diol **19** (94 mg, 0.44 mmol, 97 % yield) as a colorless oil. The diol was further purified for characterization by HPLC (50% ethyl acetate-hexanes, isocratic).

(2*E*,4*Z*,6*S*,7*S*)-methyl 7,8-dihydroxy-2,6-dimethylocta-2,4-dienoate, 19: $[\alpha]_{589}^{20}$ +13.3 ^{o} (*c* 0.57, $CHCl_3$); ^{1}H NMR 500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 12.0, 1.3 Hz, 1H), 6.41 (dd, *J* = 12.0, 11.0 Hz, 1H), 5.76 (app t, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 3.73 (d, *J* = 8.8 Hz, 1H), 3.60-3.52 (m, 2H), 2.99-2.90 (m, 1H), 2.10 (br s, 2H), 1.95 (app s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 140.5, 132.5, 128.3, 125.1, 75.4, 64.6, 51.9, 35.4, 17.1, 12.5; IR (thin film, NaCl) 3408, 2951, 1707, 1437, 1258, 1110, 1066, 998, 748, 668 cm^{-1}; LRMS (EI, Na) calcd for $C_{11}H_{18}O_4Na$, 237.12 *m/z* $(M + Na)^+$; observed, 236.97 $(M + Na)^+$ *m/z*.



Synthesis of (*S*,2*E*,4*Z*)-methyl 2,6-dimethyl-7-oxohepta-2,4-dienoate, 3: To a solution of **19** (110 mg, 0.513 mmol) in ethyl acetate (52 ml) at rt was added $Pb(OAc)_4$ (1.4 g, 3.2 mmol) in one portion. The reaction was stirred for 5 min while monitoring by TLC before adding water (5 ml) to cause the lead salts to fall out of solution. The mixture was filtered through a

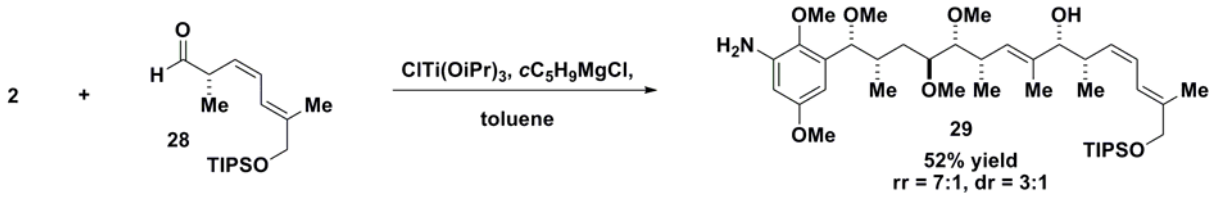
pad of florosil (~8 cm wide × 5 cm deep) rapidly and flushed with ethyl acetate (100 ml). Filtrations were repeated as necessary to remove all lead salts in order to provide a clear and colorless solution; however, it was essential to maintain a very dilute solution (< 0.01M) at all times while filtering. Upon removal of all salts, the solution was concentrated *in vacuo*, and the crude aldehyde was azeotroped with benzene (3 × 3 ml) before immediate use in the following coupling reaction.

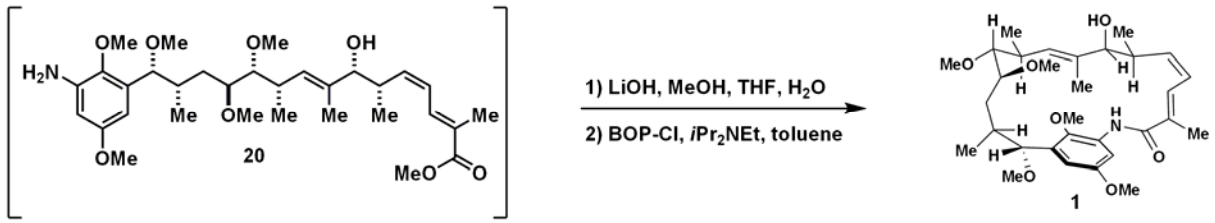


Synthesis of (2*E*,4*Z*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-methyl 15-(3-amino-2,5-dimethoxyphenyl)-7-hydroxy-11,12,15-trimethoxy-2,6,8,10,14-pentamethylpentadeca-2,4,8-trienoate, 20: To a rapidly stirring −78 °C solution of alkyne **2** (40 mg, 0.10 mmol) in 1.0 mL of toluene, was added 202 μL of ClTi(O*i*-Pr)$_3$ (1.0 M in hexanes; 0.20 mmol) and 207 μL of *c*-C_5H_9MgCl (1.95M in diethyl ether; 0.40 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting solution was slowly warmed to −30 °C where it became a dark, thick slurry which was stirred for 1 h. The slurry was then cooled to −78 °C before adding freshly prepared aldehyde **3** (60 mg, 0.30 mmol) as a solution in 400 μL of toluene. The mixture was allowed to slowly warm to rt over 1 h and was then stirred an additional 30 min at rt to provide a more homogeneous solution. The reaction was quenched with NH_4Cl (aq., sat) (1 ml). This solution was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layer was then washed with $NaHCO_3$ (aq., sat) (2 × 15 mL) and brine (1 × 15 mL), before being dried over Na_2SO_4. The crude material was purified by flash column chromatography on silica gel

eluting with 50% EtOAc-hexanes to provide **20** (42 mg, 0.073 mmol, 74 % yield) as an inseperable mixture of regioisomers and diastereomers. This mixture was carried through the following two steps.

While the selectivity was unable to be determined for the previous coupling process, a related study offers insight into the regioselectivity and diastereoselectivity of the coupling process. Alkyne **2** was coupled with a related unsaturated aldehyde **28** to provide the coupled product **29** in 52% yield (r.r. = 7:1, d.r. = 3:1).



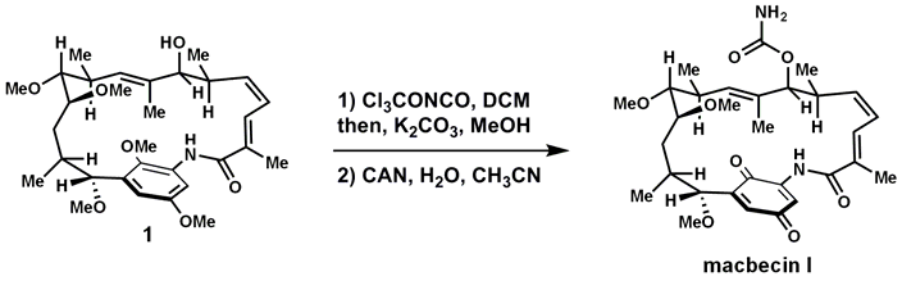


Synthesis of macrolactam, 1: To a solution of the mixture of isomers of **20** (42 mg, 0.073 mmol) in MeOH (6 ml), THF (6 ml), and water (3 ml) was added LiOH (80 mg, 1.9 mmol). The mixture was allowed to stir at rt for 18 h before the volatiles were removed *in vacuo*. The residue was dissolved in a 10% $NaHPO_4$ solution (20 ml) which was then extracted with CH_2Cl_2 (5 × 5 ml) with the aqueous layer being saturated with solid NaCl between extractions. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the aniline acid which was used crude in the cyclization.

To the aniline acid in toluene (70 ml) was added diisopropylethyl amine (203 μl, 1.16 mmol) and BOP-Cl (37 mg, 0.15 mmol) at rt. The mixture was warmed to 85 ^{o}C, and stirred at this temperature for 12 h. The solution was cooled to ambient temperature, and the solvent was removed *in vacuo*. The mixture was then purified by flash column chromatography on silica (60% ethyl acetate-hexanes) to provide **1** (18 mg, 0.033 mmol, 44% yield, 2 steps).

In spite of the fact that a mixture of regio- and diastereomers were taken into the two-step hydrolysis / cyclization sequence, the only isomer of product that we were able to isolate and characterize was that which matched Baker's intermediate, **1**.

macrolactam, 1: $[\alpha]_{589}^{20}$ +75.8 ^{o} (*c* 0.19, CH_2Cl_2); ^{1}H NMR 500 MHz, *d*-DMSO) δ 9.28 (br s, 1H), 6.61 (br s, 1H), 6.43 (d, *J* = 2.8 Hz, 1H), 5.95 (br s, 1H), 5.77 (br t, *J* = 10.9 Hz, 1H), 5.08 (br t, *J* = 10.8 Hz, 1H), 4.83 (br d, *J* = 10.1 Hz, 1H), 4.59 (d, *J* = 4.3 Hz, 1H), 4.33 (d, *J* = 5.1 Hz, 1H), 3.69 (s, 3H), 3.43 (s, 3H), 3.39 (s, 3H), 3.21 (s, 3H), 3.16 (s, 3H), 3.08 (br d, *J* = 8.4 Hz, 1H), 2.94-2.84 (m, 1H), 2.46-2.29 (m, 1H), 2.16-1.96 (m, 2H), 1.80 (s, 3H), 1.49-1.36 (m, 1H), 0.93 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.62 (d, *J* = 6.8 Hz, 3H), 0.62-0.50 (m, 1H); ^{13}C NMR (201 MHz, *d*-DMSO) δ 173.8, 155.6, 146.3, 137.8, 136.5, 134.0, 133.4, 132.7, 128.1, 124.2, 122.6, 109.5, 108.6, 84.0, 81.8, 80.7, 60.7, 60.0, 56.7, 56.3, 55.1, 35.7, 35.2, 34.8, 26.0, 18.5, 15.3, 13.4, 10.8; IR (thin film, NaCl) 3421, 2964, 2929, 2824, 1652, 1591, 1458, 1364, 1311, 1220, 1197, 1162, 1099, 1050, 1004, 736 cm^{-1}; LRMS (EI, Na) calcd for $C_{31}H_{47}NO_7Na$, 568.34 *m/z* $(M + Na)^+$; observed, 568.66 $(M + Na)^+$ *m/z*.



Synthesis of macbecin I: To a stirring solution of macrolactam **1** (23 mg, 0.042 mmol) in dichloromethane (4 ml) was added trichloroacetylisocyanate (30 μl, 0.25 mmol). After 30 min at rt, the reaction mixture was concentrated, then, methanol (2 ml) and K_2CO_3 (50 mg) were added. After 2 h at rt, the methanol was evaporated *in vacuo*, and the residue was filtered through a short pad of silica eluting with 70% ethyl acetate-hexanes to provide the desired carbamate of suitable purity for the following reaction.

The carbamate was dissolved in CH_3CN/H_2O (9:1, 20 ml) and an aqueous solution of cerium ammonium nitrate (1N, 210 μl) was added at 0 ^oC. After 30 min the solution was diluted with water (10 ml) and the aqueous layer was extracted with dichloromethane (5 × 5 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (ether) to provide macbecin I (8 mg, 0.015 mmol, 35 % yield, 2 steps) as a yellow solid. The residue was further purified for characterization by HPLC (50 % ethyl acetate-hexanes, isocratic).

(+)-macbecin I: $[\alpha]_{589}^{20}$ +346 ^{o} (*c* 0.18, $CHCl_3$); ^1H NMR 500 MHz, $CDCl_3$) δ 8.88 (br. s, 1H), 7.33 (d, *J* = 2.5 Hz, 1H), 7.12 (d, *J* = 11.9 Hz, 1H), 6.60 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.33 (dt, *J* = 12.2, 1.9 Hz, 1H), 5.80 (br s, 1H), 5.66 (dd, *J* = 10.7, 6.9 Hz, 1H), 5.25 (br s, 1H), 4.62 (br. s, 2H), 4.57 (br s, 1H), 3.54 (br s, 1H), 3.52 (s, 3H), 3.32 (s, 3H), 3.29 (s, 3H), 3.32-3.18 (m, 1H), 3.13-3.04 (m, 1H), 2.57-2.39 (m, 1H), 1.98 (s, 3H), 1.77-1.60 (m, 2H), 1.49 (m, 1H), 1.48 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H);

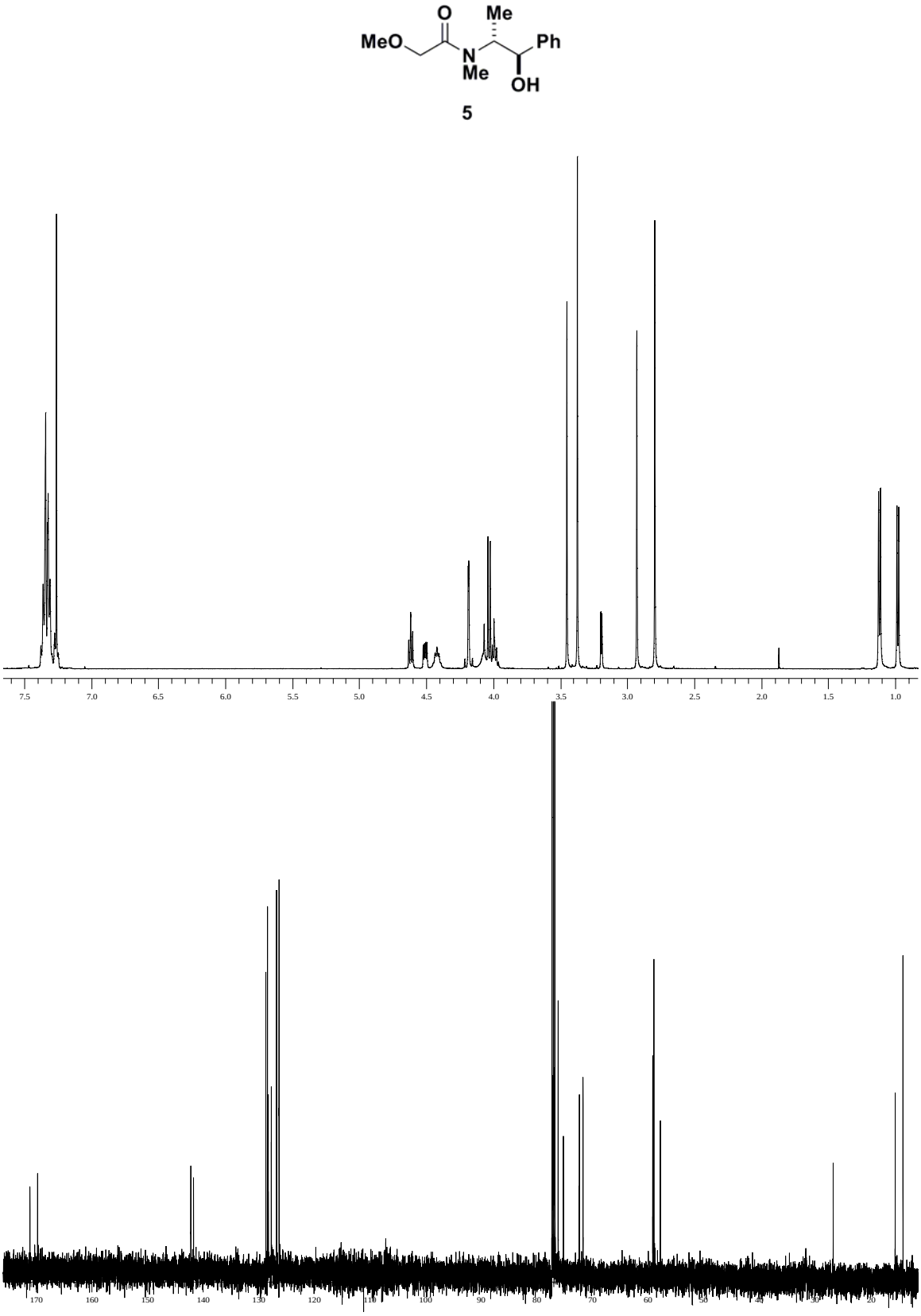
^{13}C NMR (126 MHz, $CDCl_3$) δ 187.9, 184.0, 169.2, 155.8, 144.9, 141.2, 138.2, 133.2, 132.3, 131.6, 129.0, 127.6 (br), 124.2, 112.9, 83.6, 83.0, 79.2, 77.1, 60.3, 58.3, 55.6, 34.7, 33.9, 33.5, 17.3, 15.0, 13.4, 13.2, 12.4; IR (thin film, NaCl) 3427, 3359, 2968, 2928, 1733, 1695, 1662, 1648, 1610, 1506, 1456, 1386, 1315, 1259, 1208, 1092, 1030 cm^{-1}; LRMS (EI, Na) calcd for $C_{30}H_{42}N_2O_8Na$, 581.29 *m/z* $(M + Na)^+$; observed, 581.46 $(M + Na)^+$ *m/z*.

Total Synthesis of Macbecin I

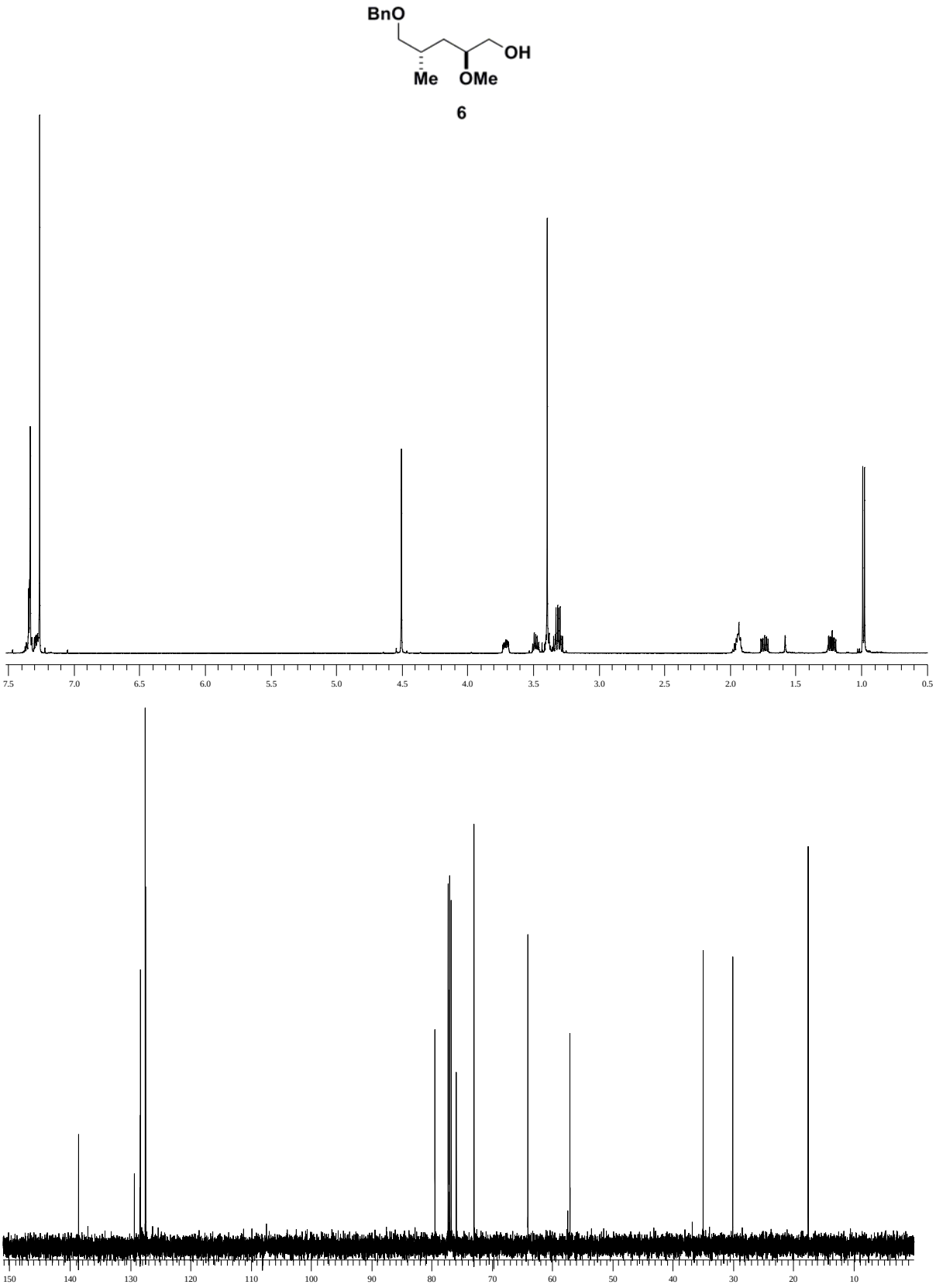
Justin K. Belardi and Glenn C. Micalizio

SUPPORTING INFORMATION-2:

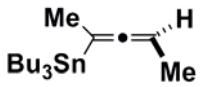
Spectral Data for Compounds 1-2, 5-9, 11-13, 16, 18-19, 25, 27



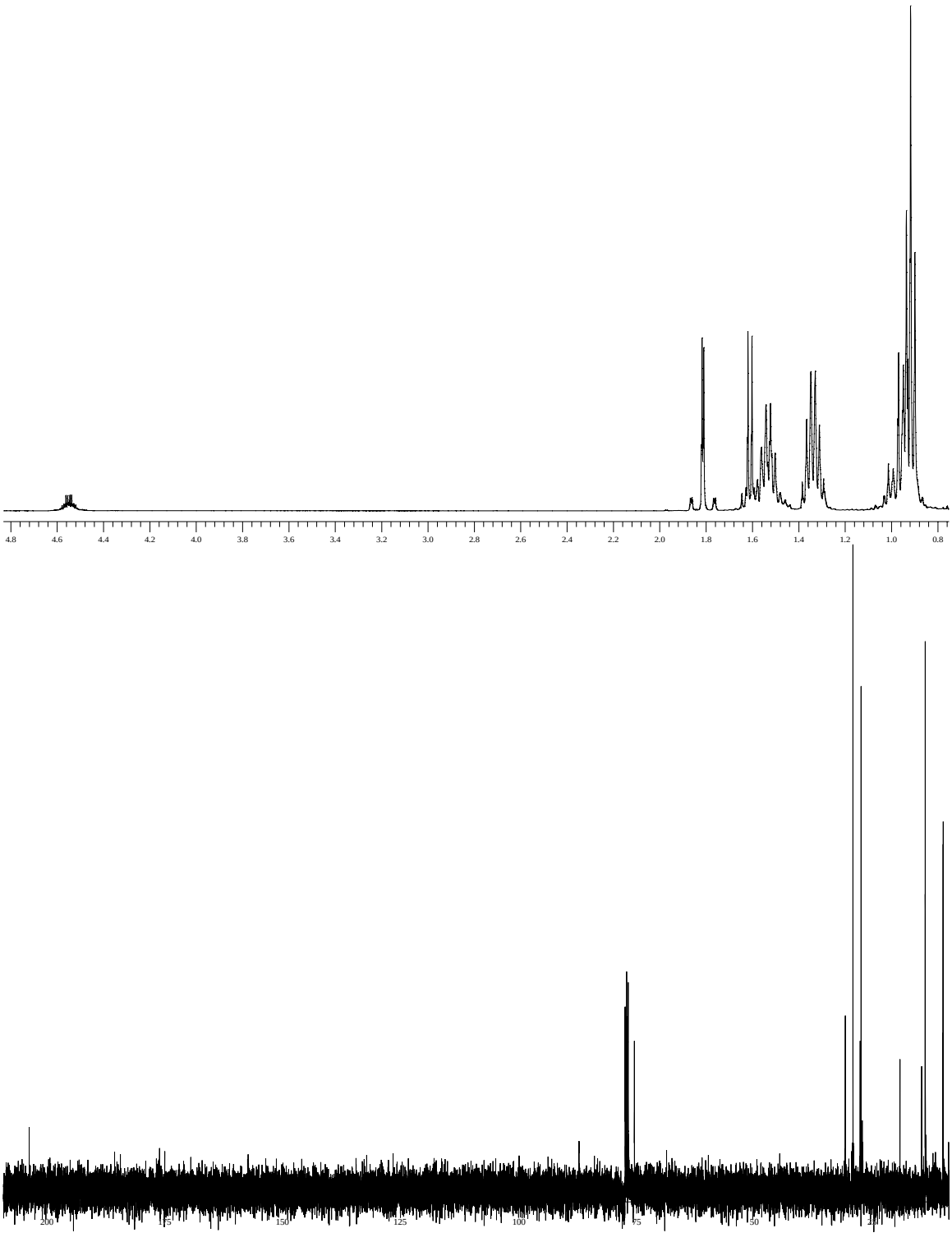
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **5** ($CDCl_3$)



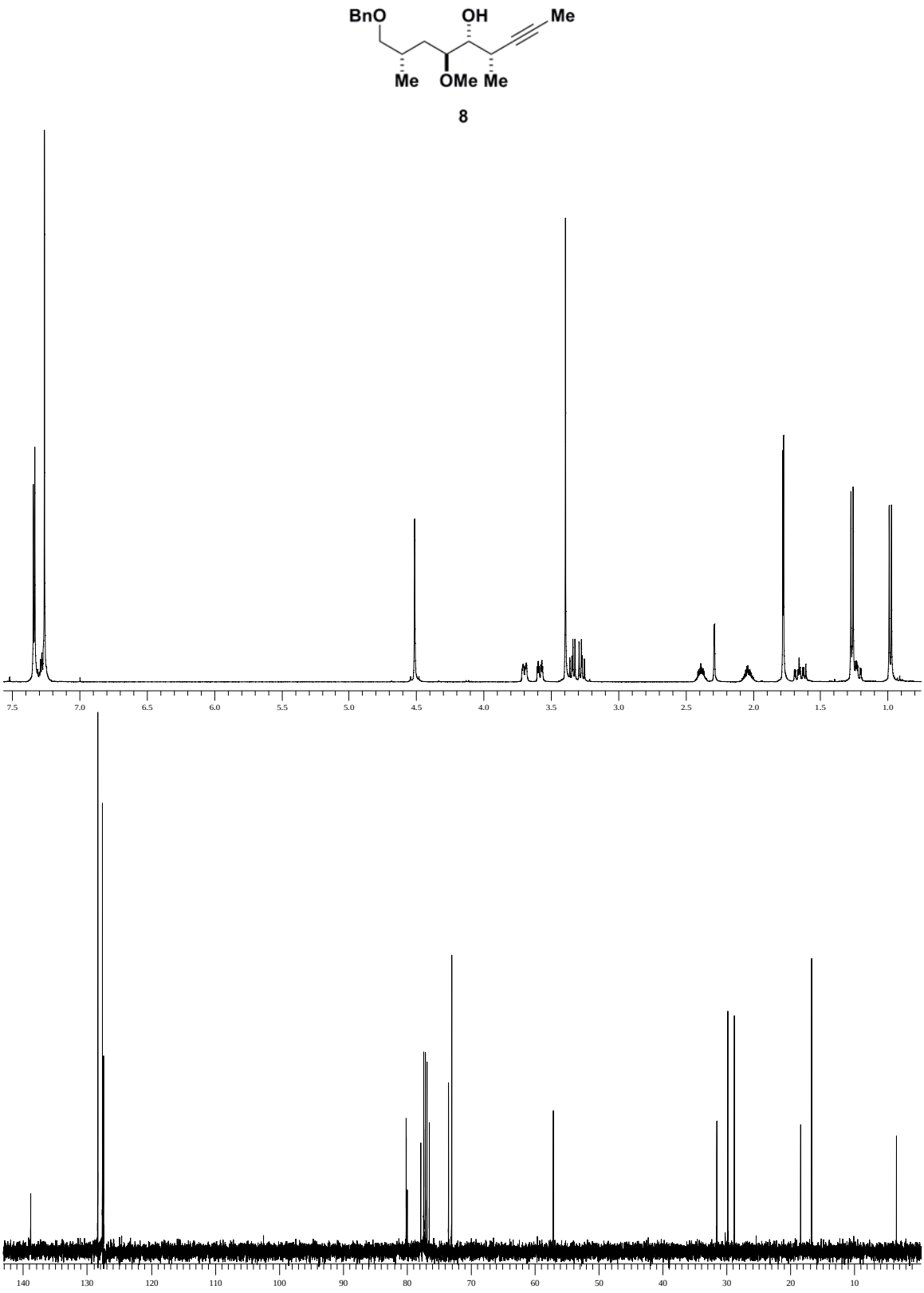
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **6** ($CDCl_3$)



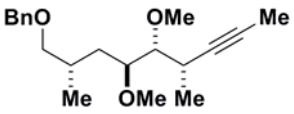
7



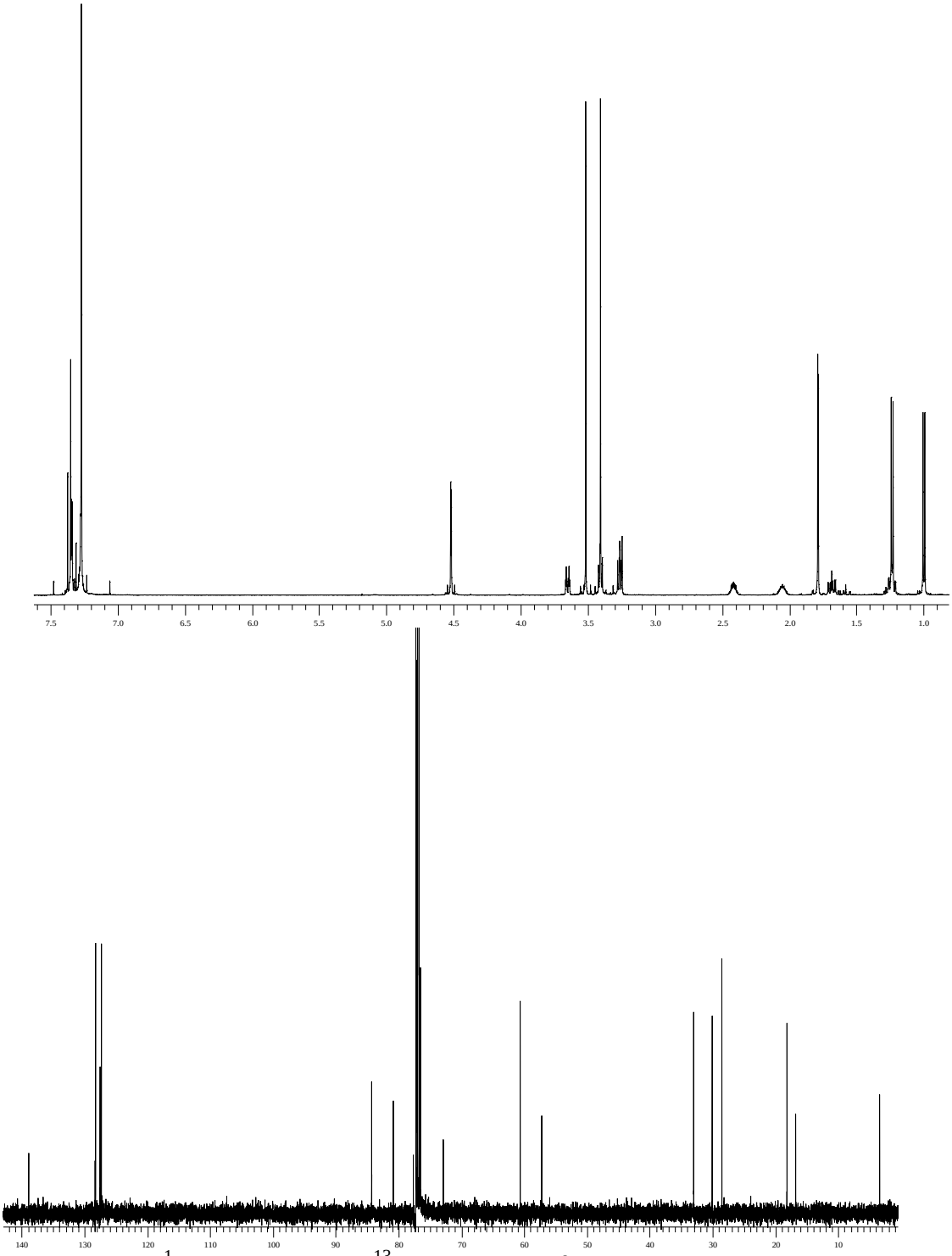
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **7** ($CDCl_3$)



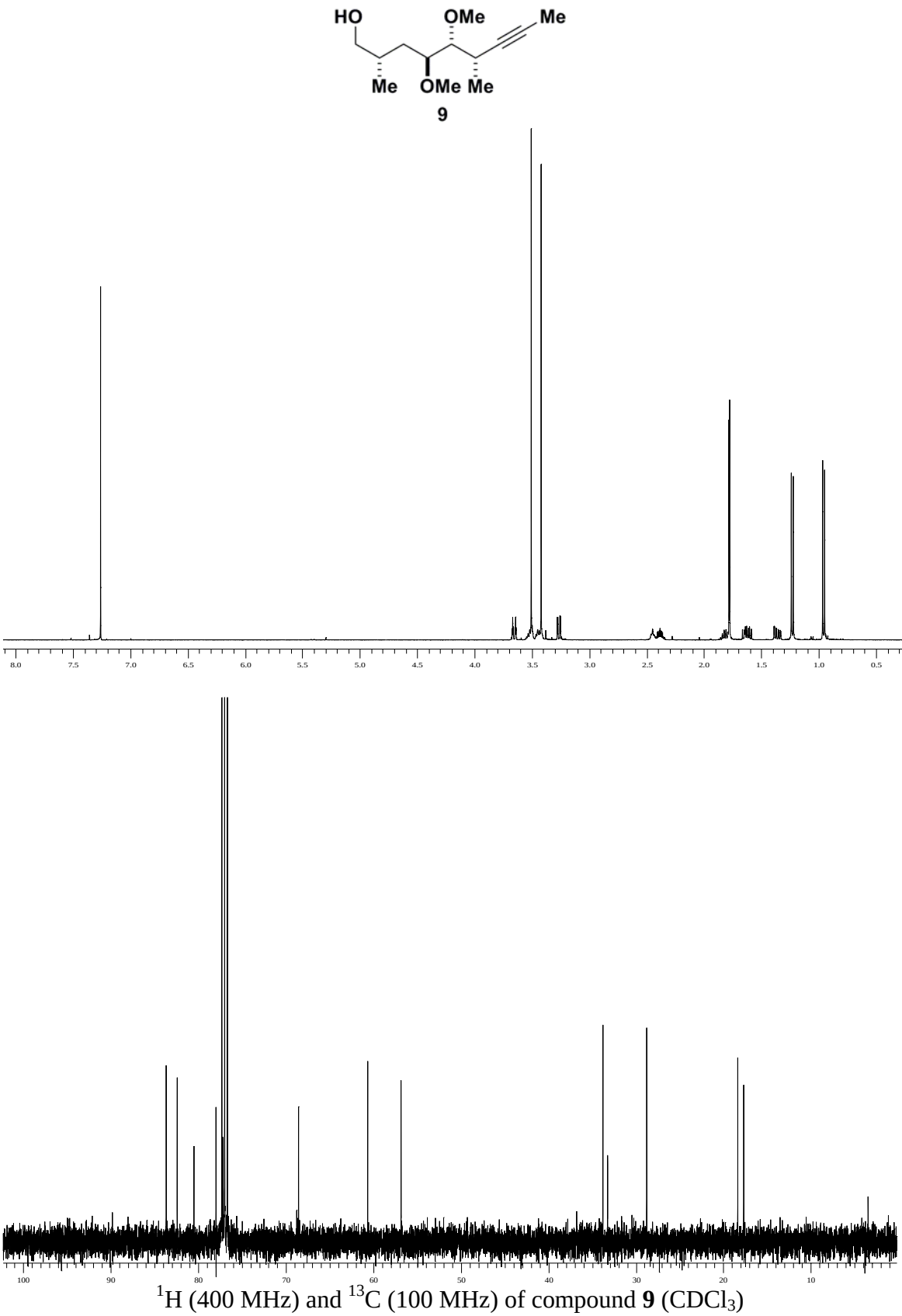
^{1}H (400 MHz) and ^{13}C (126 MHz) of compound **8** ($CDCl_3$)



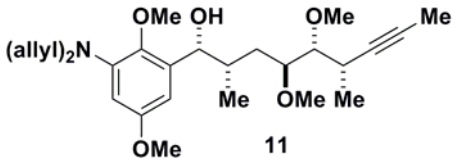
25



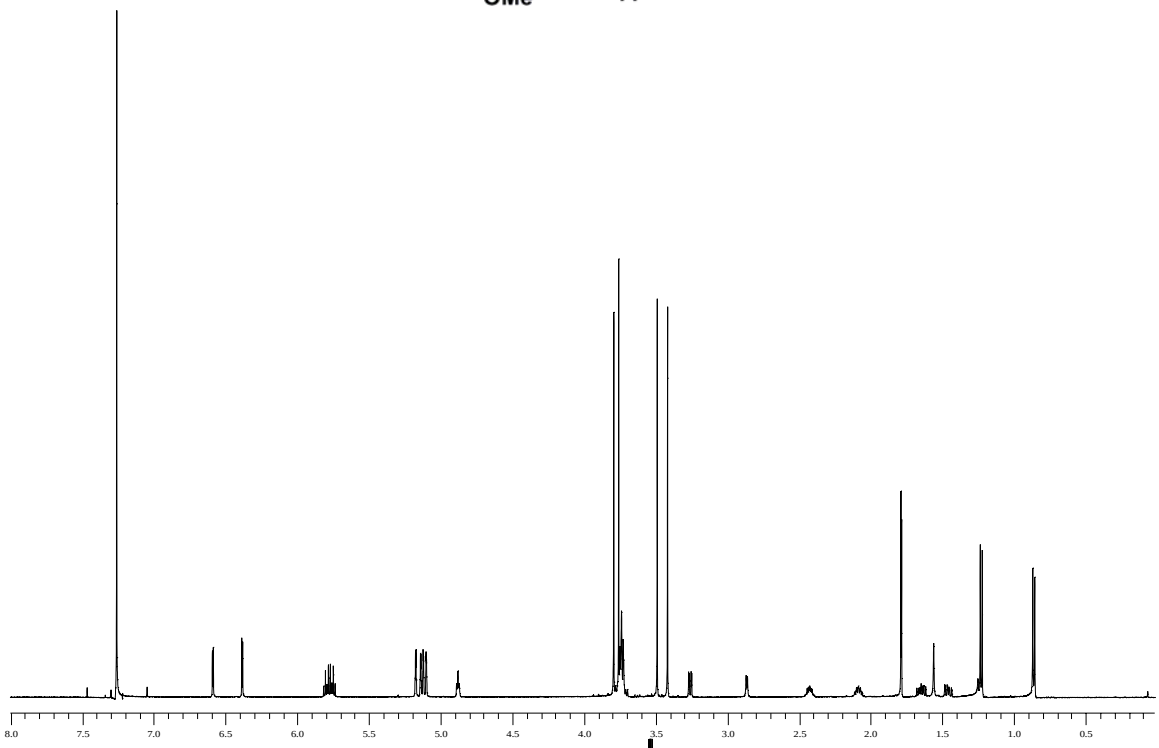
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **25** ($CDCl_3$)

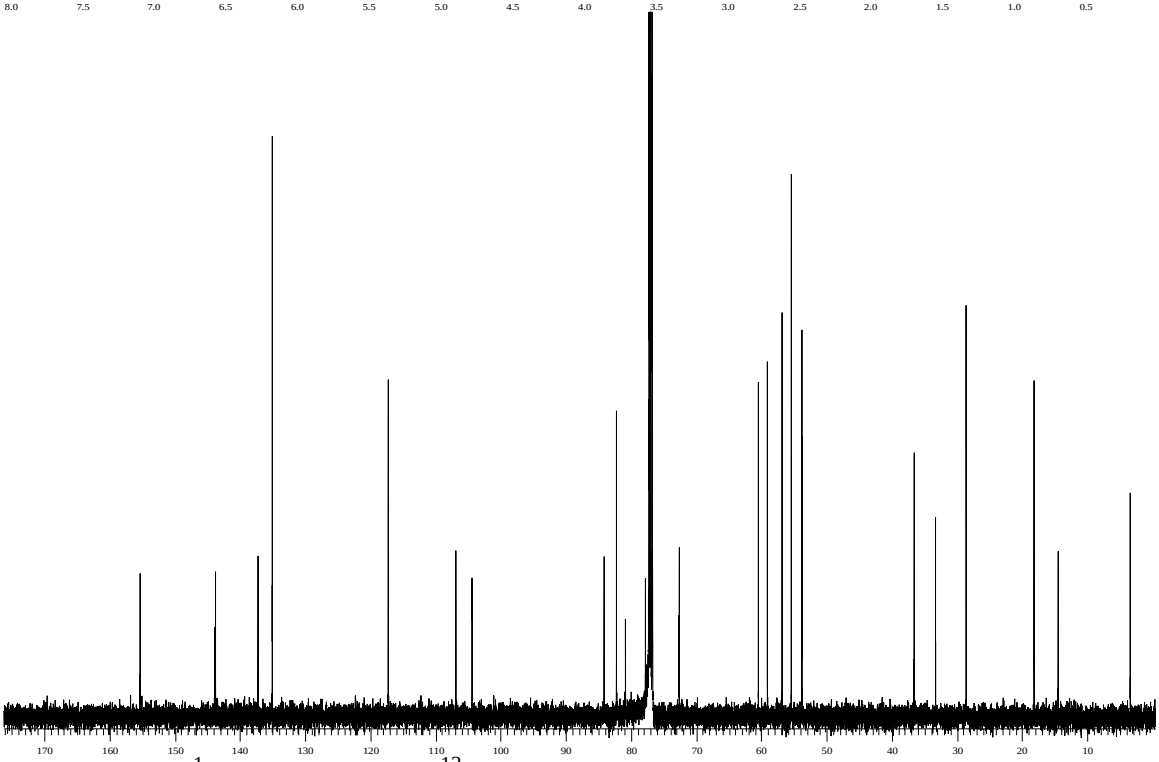


^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **9** ($CDCl_3$)

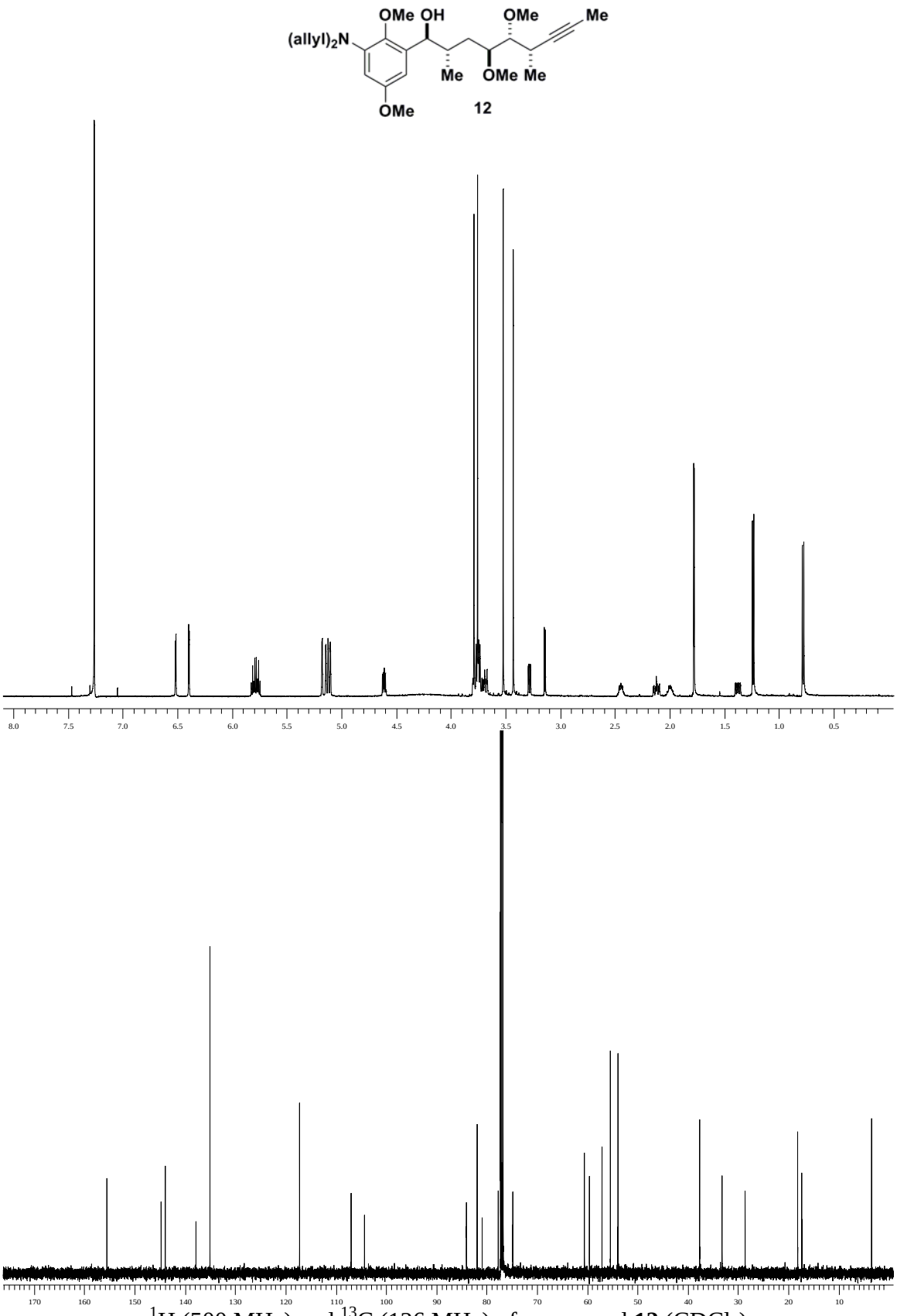


11

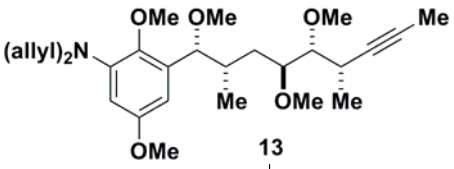




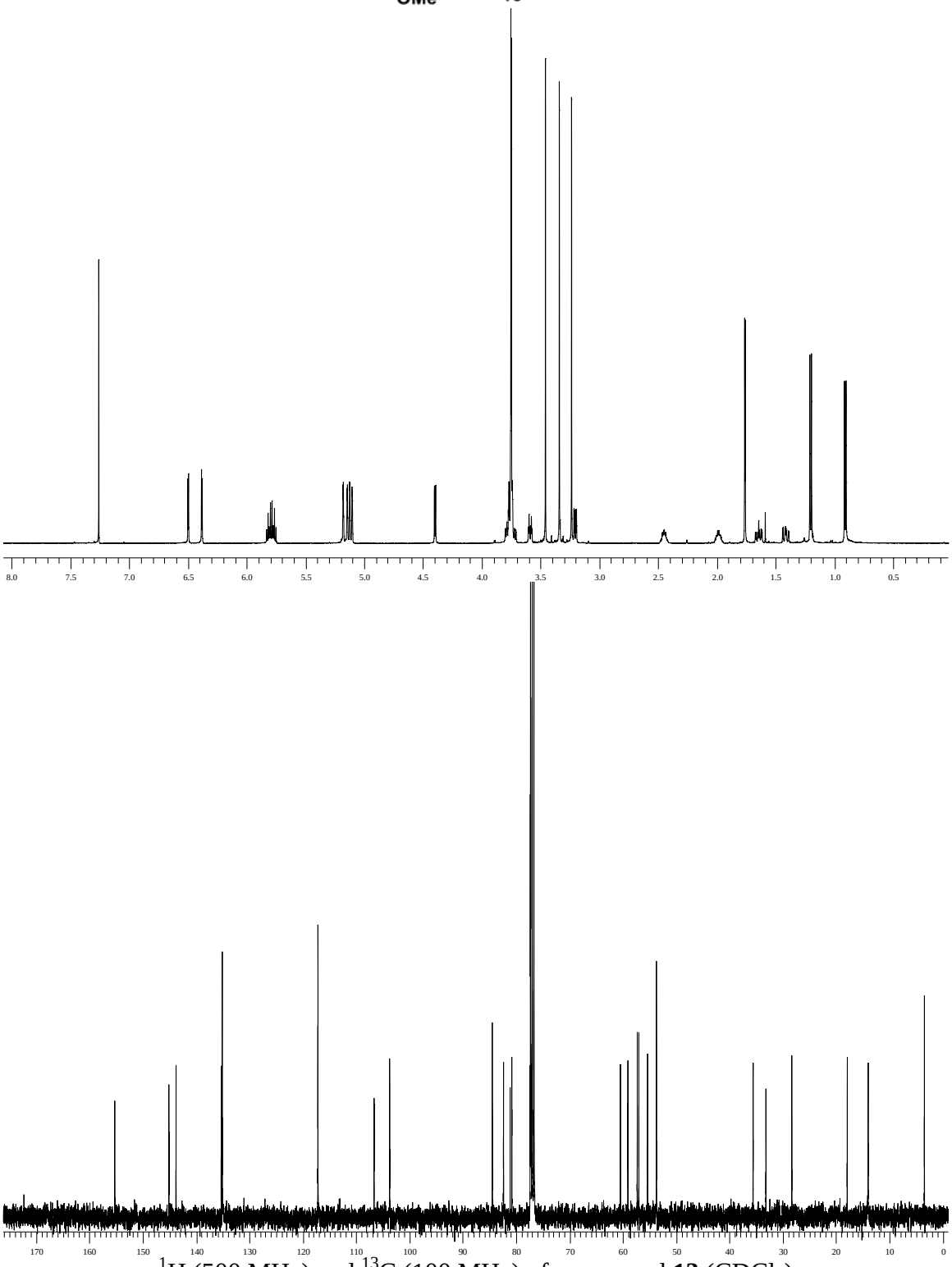
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **11** ($CDCl_3$)



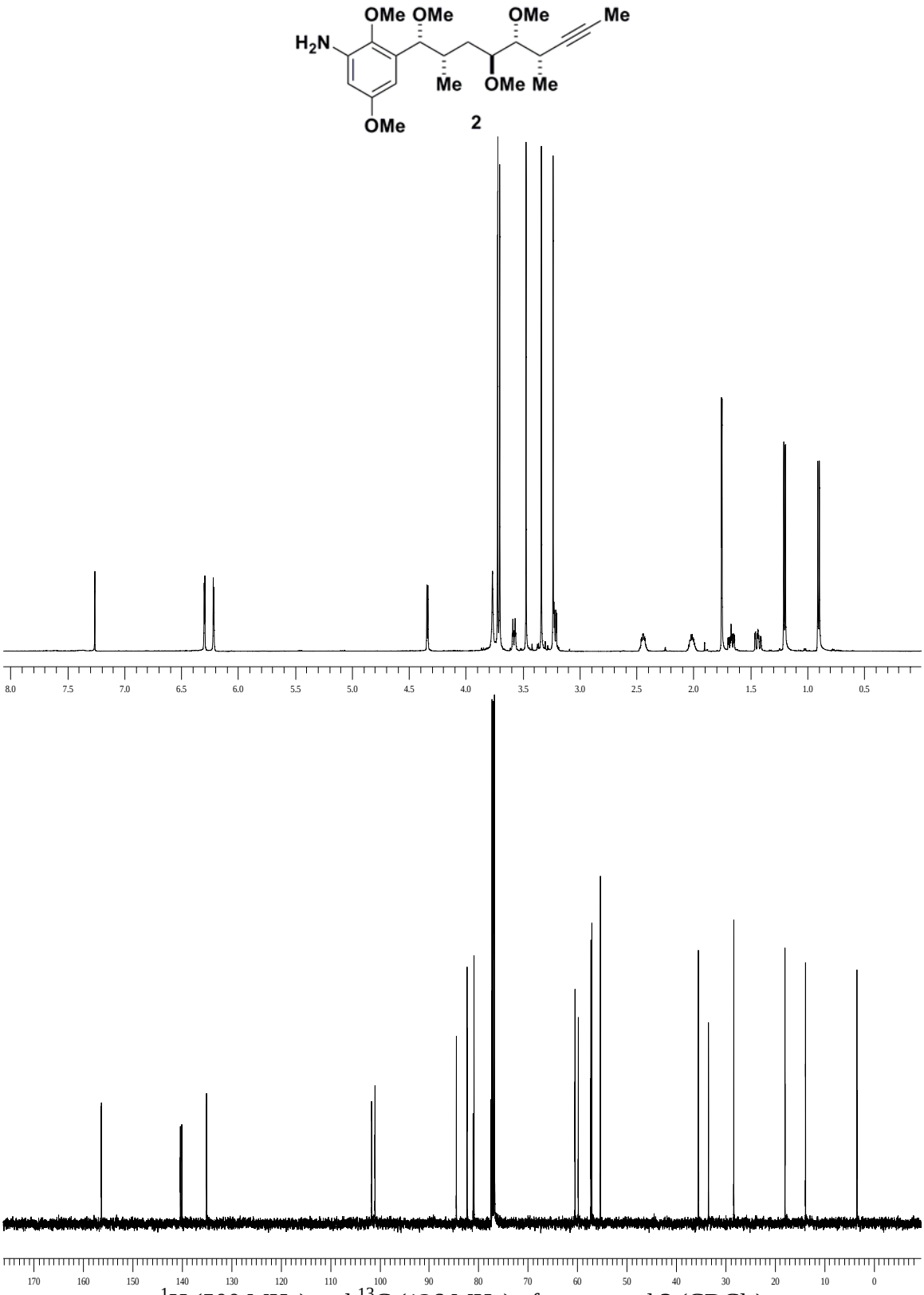
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **12** ($CDCl_3$)



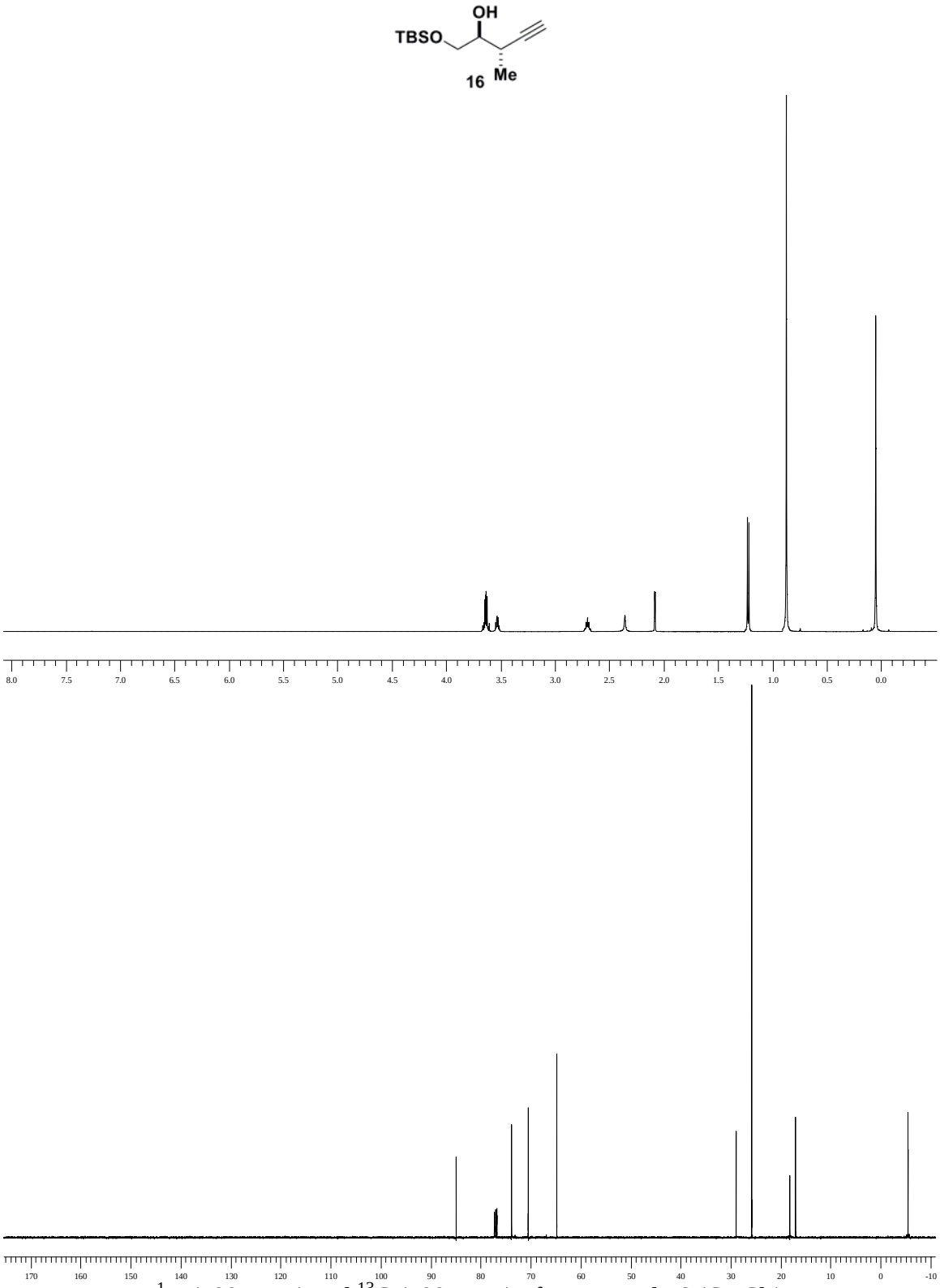
13



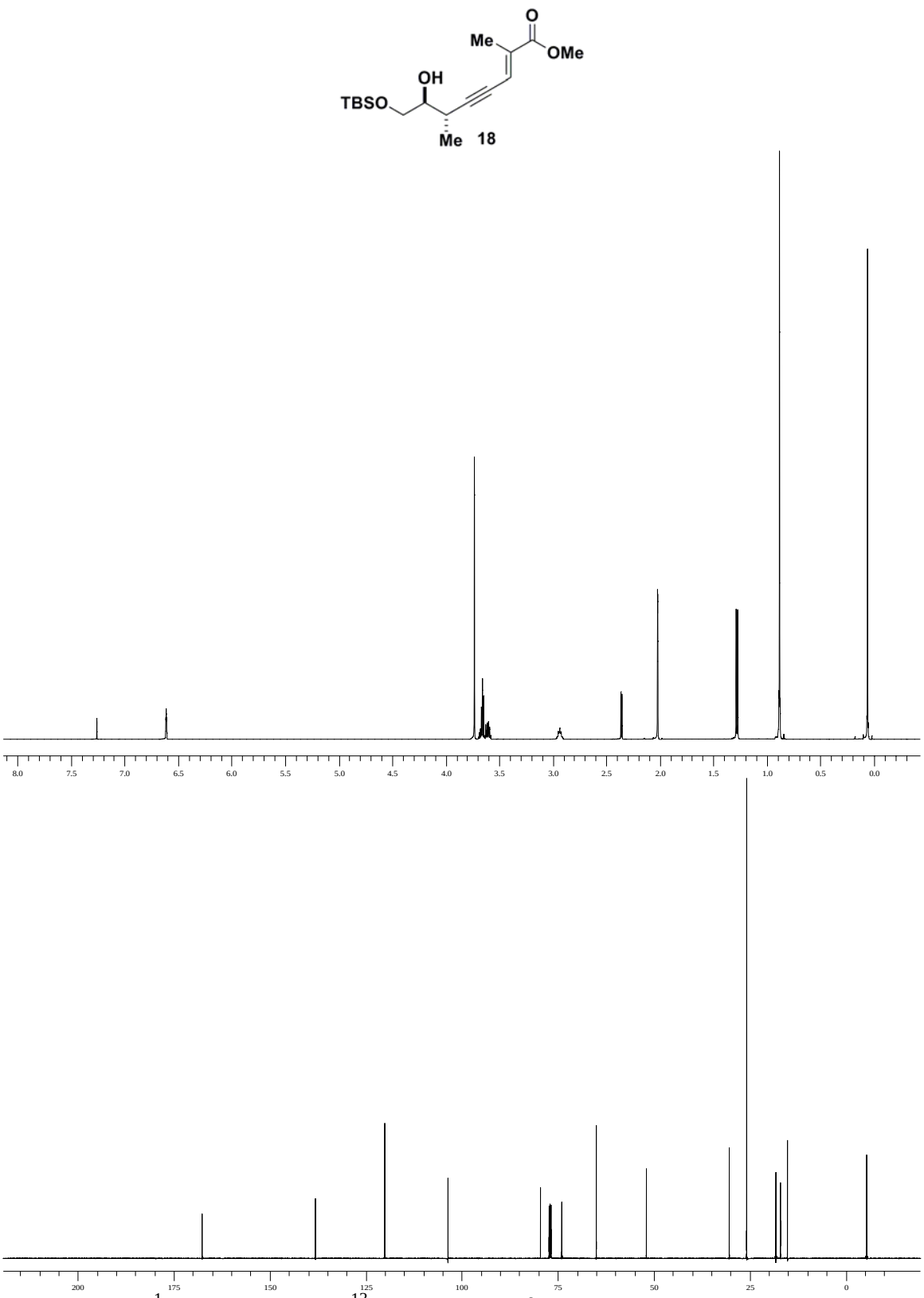
^{1}H (500 MHz) and ^{13}C (100 MHz) of compound **13** ($CDCl_3$)



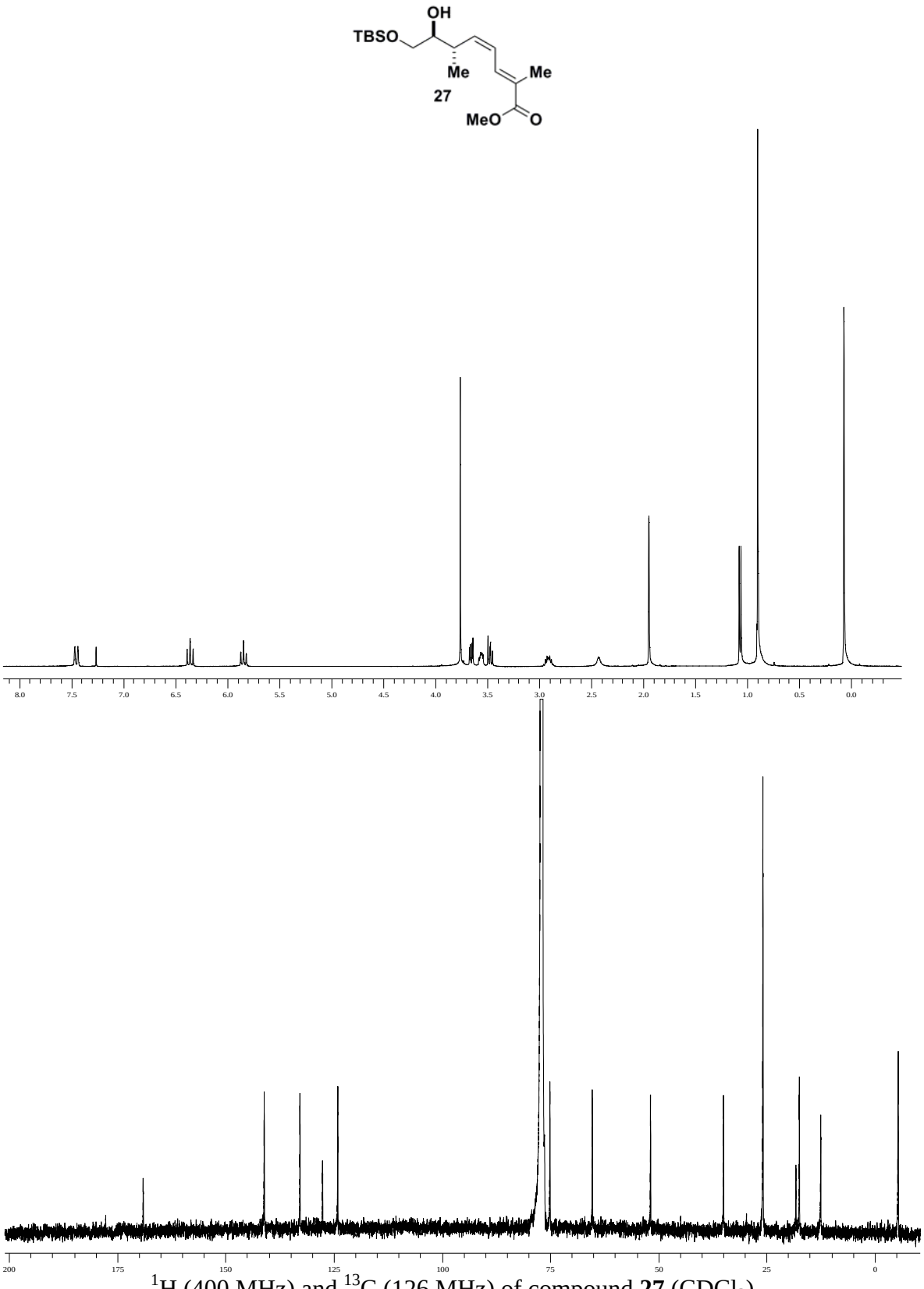
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **2** ($CDCl_3$)



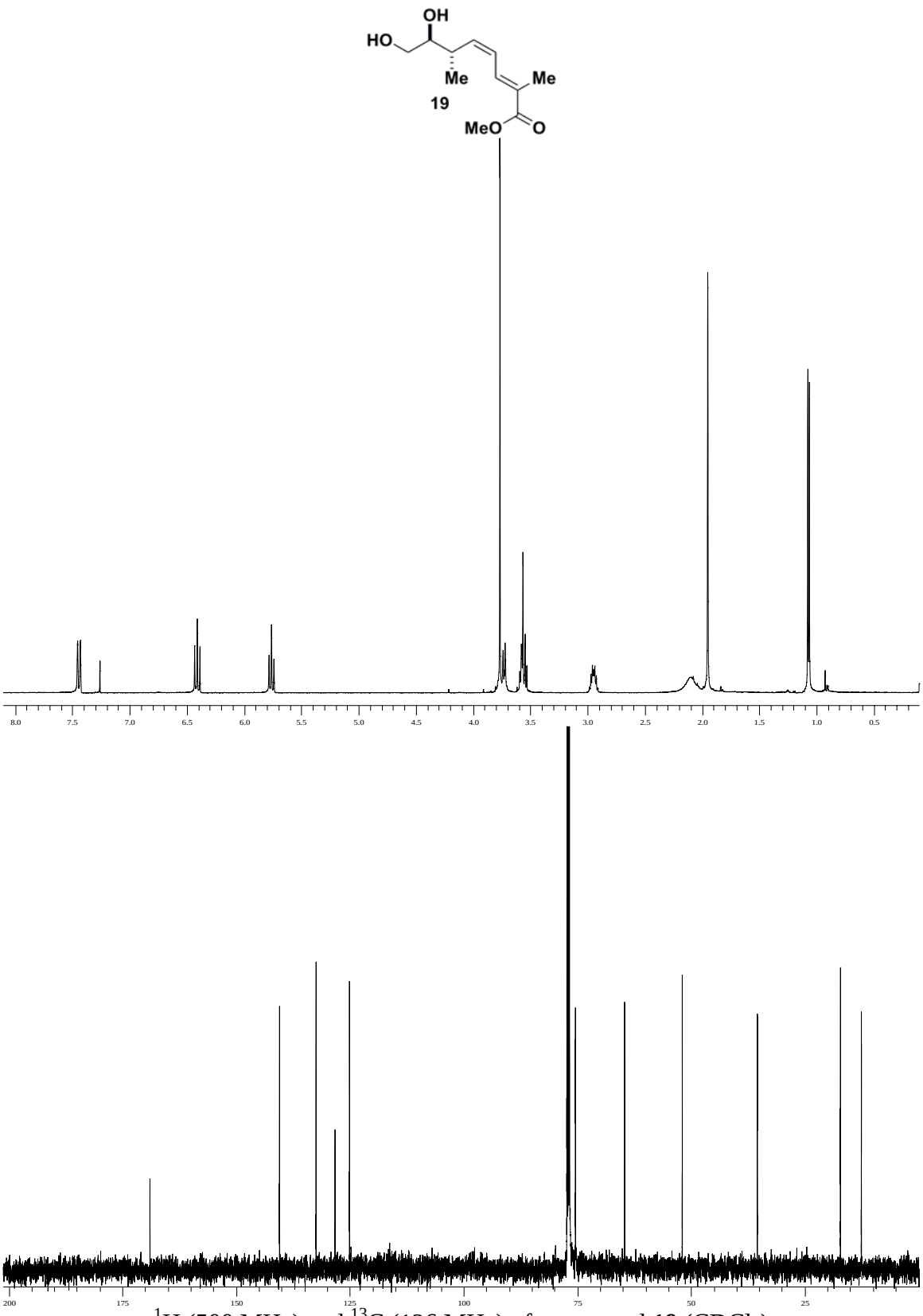
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **16** ($CDCl_3$)



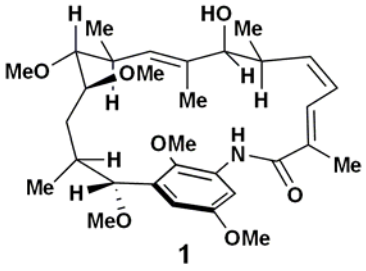
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **18** ($CDCl_3$)



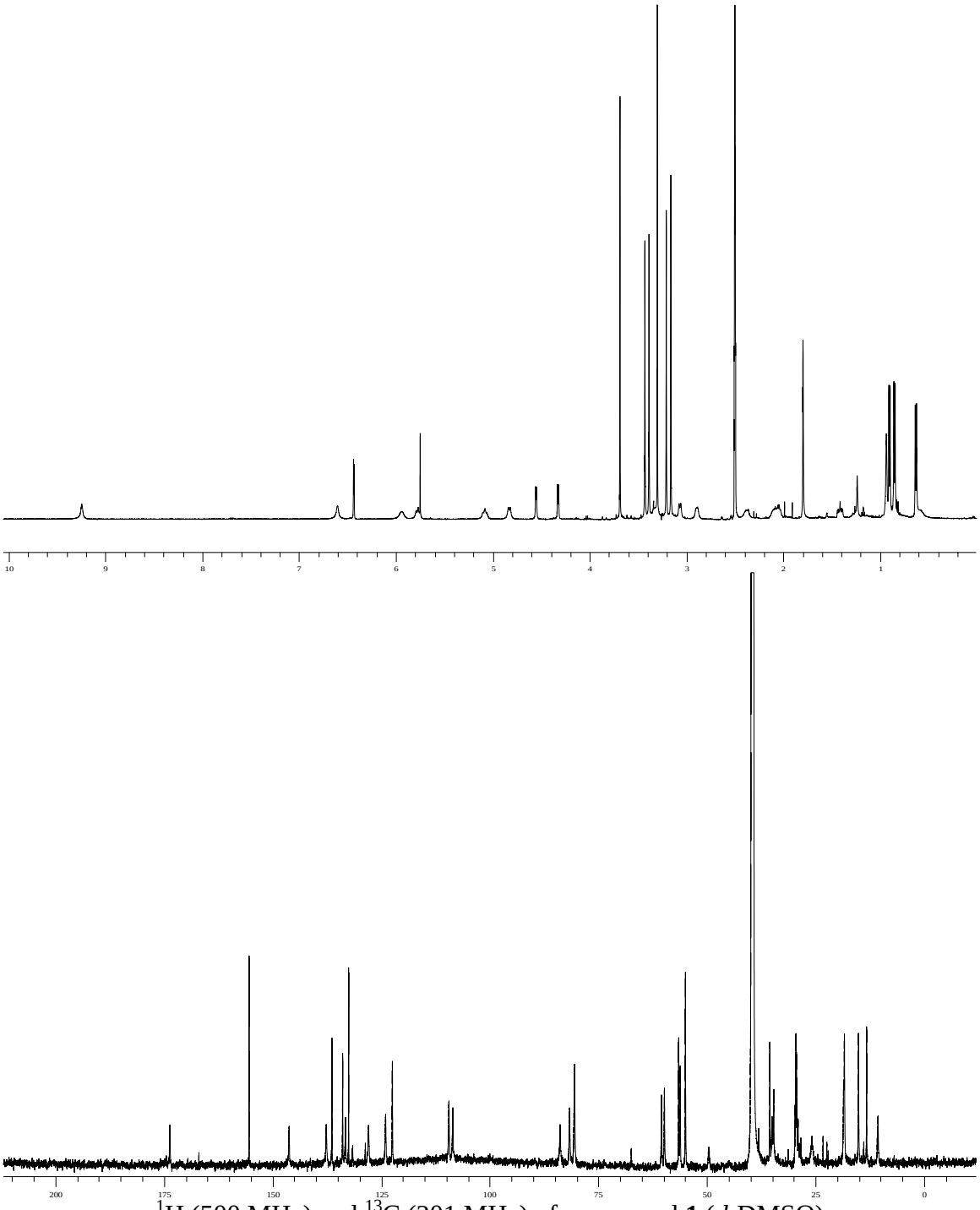
^{1}H (400 MHz) and ^{13}C (126 MHz) of compound **27** ($CDCl_3$)



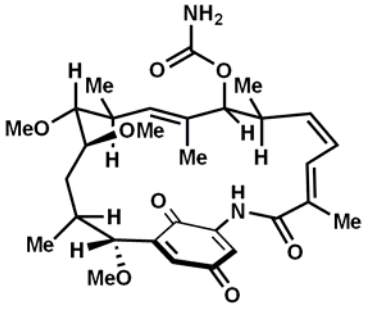
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **19** ($CDCl_3$)



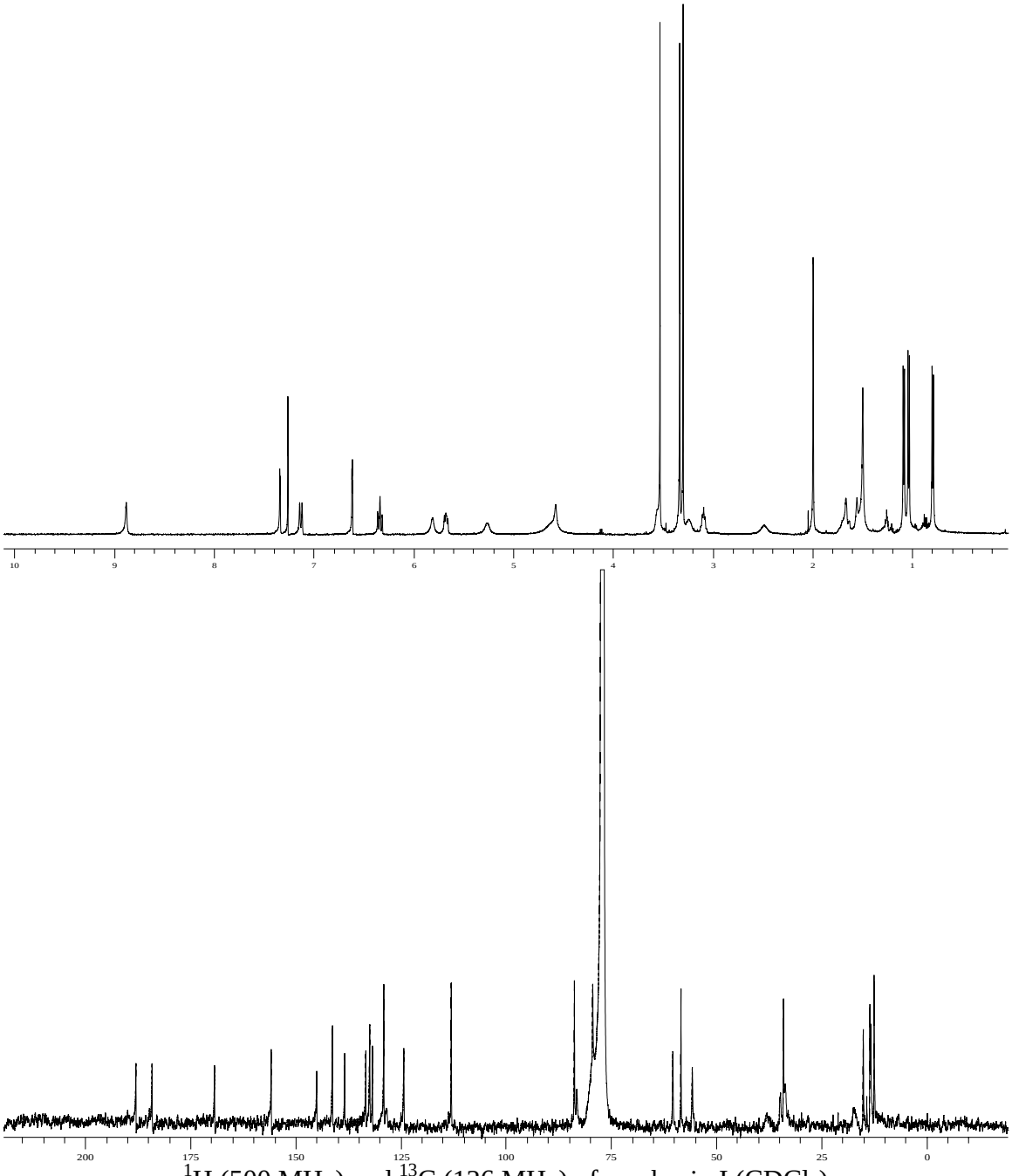
1



^{1}H (500 MHz) and ^{13}C (201 MHz) of compound **1** (*d*-DMSO)

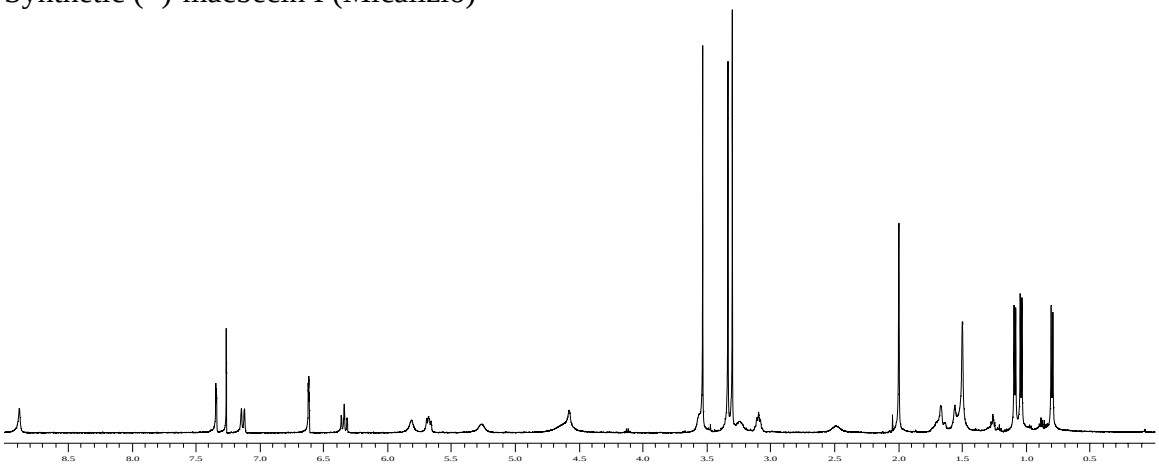


macbecin I

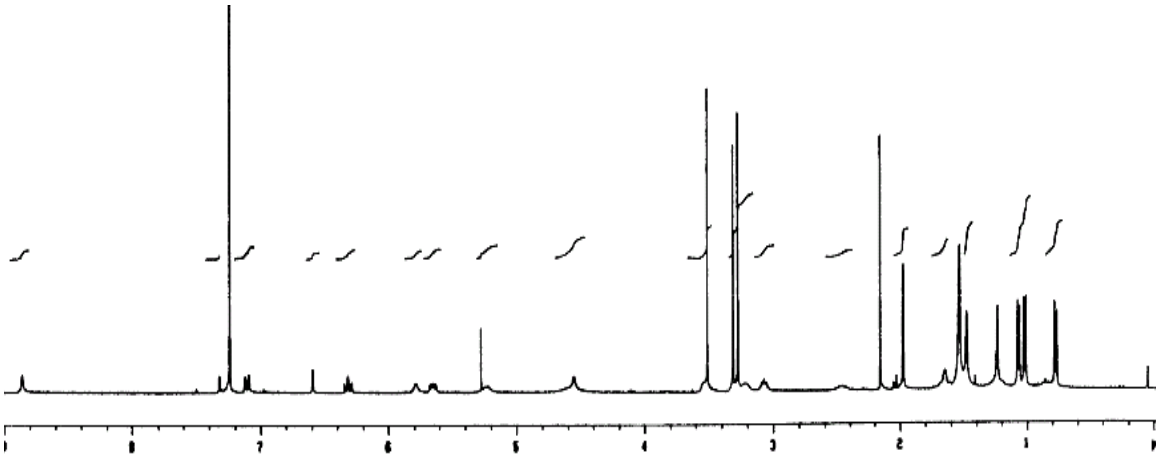


^{1}H (500 MHz) and ^{13}C (126 MHz) of macbecin I ($CDCl_3$)

Synthetic (+)-macbecin I (Micalizio)



Synthetic (+)-macbecin I (Panek)
J. S. Panek, F. Xu, A. C. Rondon, *J. Am. Chem. Soc.* **1998**, *120*, 4113-4122.



Synthetic and natural (+)-macbecin I (Evans)
D. A. Evans, S. J. Miller, M. D. Ennis, *J. Org. Chem.* **1993**, *58*, 471-485.