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Supporting Information

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The Enantioselective Synthesis of Phomopsin B

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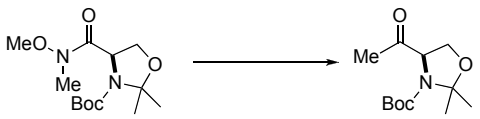
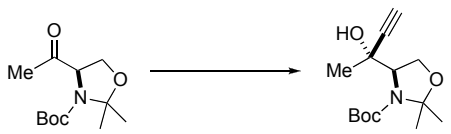
Experimental Procedures

NMR spectra were recorded on Varian UI-500 (499.8 MHz for ^{1}H, 125.7 MHz for ^{13}C) and AM-400 (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane using the solvent resonance as an internal standard (chloroform, 7.26 ppm in ^{1}H NMR and 77.0 ppm in ^{13}C NMR; methanol, 3.30 ppm in ^{1}H NMR and 49.0 ppm in ^{13}C NMR; dimethyl sulfoxide, 2.49 ppm in ^{1}H and 39.5 ppm in ^{13}C). Infrared spectra were recorded on a Thermo Nicolet IR300 Sprectrometer and are reported in wavenumbers (cm^{-1}). Mass spectral data was acquired at the Stanford University Vincent Coates Foundation Mass Spectrometry Laboratory. Tetrahydrofuran (THF), dichloromethane, acetonitrile, toluene, and ether were either taken from a solvent purification system or distilled with the appropriate drying agent and scavenger when applicable. *N*,*N*-Dimethylformamide (DMF) and 1,4-dioxane were purchased in bottles sealed with septa. Triethylamine, *N*,*N*-diisopropylethylamine, pyridine, and 2,6-lutidine were distilled over calcium hydride. Unless stated otherwise, all reagents were used without purification and each reaction began by evacuating and purging the starting material with nitrogen in the reaction vessel.



(*R*) 4-Acetyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine. A 1000-mL flask containing Weinreb amide (35.6 g, 123.5 mmol, 1 equiv) was dissolved in THF (350 mL). After cooling to -78 ˚C, methyllithium (1.6 M in diethyl ether, 154.3 mL, 246.9 mmol, 2 equiv) was added dropwise *via* cannula over 1 h. The solution was stirred an additional 1 h before quenching with a saturated ammonium chloride solution (200 mL). The icy mixture was warmed to room temperature and then diluted with water (50 mL) before separating the two layers. The aqueous layer was then extracted with diethyl ether (3 × 150 mL). The organic extracts were combined and dried over anhydrous sodium sulfate before removing solvent under reduced pressure to leave a brownish oil weighing 40 g. This crude oil was purified using 900 mL of silica gel by column chromatography using 9:1 hexanes/ethyl acetate to elute the desired methyl ketone (20.3 g, 83.4 mmol, 68%). All spectral properties matched literature values.[1]

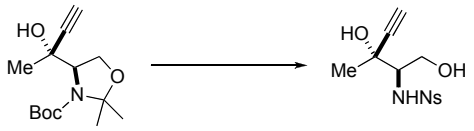


(*4R*,*2'R*) 4-(2-Hydroxybut-3-yn-2-yl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidine. To a 1000-mL flask containing the methyl ketone (19.4 g, 79.7 mmol, 1 equiv) was added THF (250 mL). Ethynylmagnesium bromide (0.5 M in THF, 478 mL, 239.2 mmol, 3 equiv) was then added dropwise *via* cannula. After stirring for 1 h at room temperature, the reaction was quenched with saturated ammonium chloride (500 mL) and then diluted with diethyl ether (250 mL). The layers were separated and then the aqueous layer was extracted with diethyl ether (3 × 250 mL). The organic extracts were combined, washed with brine (300 mL), and dried over anhydrous sodium sulfate. Solvent was removed *in vacuo* to give 22 g of a crude off-white oil. This was purified by silica gel column chromatography using 9:1 hexanes/ethyl acetate to provide the desired tertiary alcohol (19.5 g, 72.4 mmol, 91%) as a 9.5:1 mixture of (*2'R*) and (*2'S*) alcohol diastereomers as measured by peak integration by ^{1}H NMR in DMSO-d_6 at 100 ˚C.

TLC R_f = 0.6 (2:1 hexanes/ethyl acetate)

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 5.26 (s, 1H), 4.13 (dt, J=5, 8 Hz, 1H), 3.97 (dd, J=7, 10 Hz, 2H), 3.02 (s, 1H), 1.59 (s, 3H), 1.47 (s, 9H), 1.46 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C) δ 153.3, 94.3, 87.0, 79.6, 73.0, 69.3, 64.4, 64.2, 27.5, 27.0, 26.2, 23.3.



(*2R*,*4R*)-*N*-(2-Hydroxy-1-hydroxymethyl-2-methyl-but-3-ynyl)-2-nitro-benzenesulfonamide. To a 1000-mL flask was added acetonide (19.3 g, 71.7 mmol, 1 equiv), dichloromethane (500 mL), and concentrated hydrochloric acid (33 mL, 335 mmol, 4.7 equiv). After 1.5 h, the volatiles were removed under reduced pressure to afford a crude brown oil. To this oil was added THF (300 mL), water (100 mL), and magnesium oxide (14.44 g, 358.3 mmol, 5 equiv). Upon addition of the oxide base, a considerable exotherm was evolved that was tempered by immersing the reaction flask into a 0 ˚C bath. Once the solution had returned to room temperature, 2-nitrobenzenesulfonyl chloride (13.93 g, 78.9 mmol, 1.1 equiv) was added dropwise *via* cannula as a solution in THF (100 mL) over 1 h and then stirred an additional hour. Another aliquot of 2-nitrobenzenesulfonyl chloride (3.8 g, 21.5 mmol, 0.3 equiv) was added directly and the mixture was stirred an additional 1 h. The reaction was then diluted with CH_2Cl_2 (500 mL) before quenching with pH 2.5 phosphate buffer (500 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 250 mL). The organic extracts were combined and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to afford 24 g a crude brown foam. Silica gel column chromatography was used to purify the desired sulfonamide using a mobile phase gradient of 3:1 to 2:1 to 1:1 hexanes/ethyl acetate. Multiply sulfonylated byproducts eluted first, followed by the desired product. Then 5:1 chloroform/methanol completed elution of the desired benzenesulfonamide (19.4 g, 61.7 mmol, 86%).

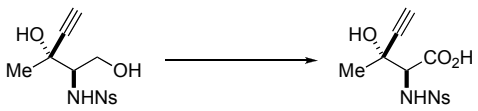
TLC R_f = 0.6 (5:1 chloroform/methanol)

IR (film): 3291 m, 2932 w, 1541 s, 1357 s, 1167 s, 1089 m, 784 w, 735 m, 655 m, 591 m.

^{1}H NMR (499.8 MHz, $CDCl_3$) δ 8.17-8.15 (m, 1H), 7.91-7.88 (m, 1H), 7.77-7.72 (m, 1H), 6.00 (d, J=9 Hz, 1H), 3.89 (dd, J=5, 6 Hz, 2H), 3.60 (dt, J=5, 9 Hz, 1H), 3.18 (s, 1H), 2.37 (s, 1H), 2.31 (t, J=6 Hz), 1.54 (s, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 147.7, 134.8, 133.6, 133.0, 130.6, 130.3, 125.4, 86.5, 84.1, 79.6, 73.9, 70.5, 63.2, 61.7, 60.4, 28.0, 14.2.

HRMS calculated for $C_{12}H_{14}N_2O_6S$ (M+Na): 337.0470 amu, found (ESI) 337.0465 amu.



(*2S*,*3R*)-3-Hydroxy-3-methyl-2-(4-nitro-benzenesulfonyl-amino)-pent-4-ynoic acid.

To a 1000-mL flask containing the Nosyl protected amine (18.9 g, 60.1 mmol, 1 equiv) was added acetonitrile (190 mL), pH 7 phosphate buffer (143 mL), and TEMPO (658 mg, 4.2 mmol, 0.07 equiv). The flask contents were heated to 35 ˚C at which time sodium chlorite (13.59 g, 120.2 mmol, 2 equiv) and 5.25% sodium hypochlorite (1.6 mL, 1.20 mmol, 0.02 equiv) were diluted as aqueous solutions (38 mL and 19 mL, respectively). Simultaneous dropwise addition of these solutions was effected by a syringe pump over a period of 2 h. (Caution: Do not premix these two solutions prior to addition to the reaction flask). After 3 h, the reaction took on a dark red color that persisted for the duration of the reaction. After 26 h, the reaction was cooled to room temperature and diluted with water (285 mL). Using ~30 mL of 2.0 N NaOH, the pH was adjusted to 8. Sodium sulfite (18.3 g, 145.2 mmol, 2.4 equiv) was added as an aqueous solution (190 mL) before readjusting the pH back to 8.5-9.0 using 2.0 N NaOH and stirring an additional 30 min. The mixture was next washed with hexanes (185 mL) and toluene (3 × 185 mL). The aqueous layer was then acidified to pH 3.5 using 3.0 N HCl (30 mL) before extracting it with CH_2Cl_2 (8 × 250 mL) and diethyl ether (16 × 250 mL). The aqueous layer was then acidified further to pH 1 and extracted further using ethyl acetate (10 × 500 mL). The organic extracts were combined and dried over anhydrous sodium sulfate before removing solvent *in vacuo* to leave a white foam identified as the desired acid (15.1 g, 46.0 mmol, 76%).

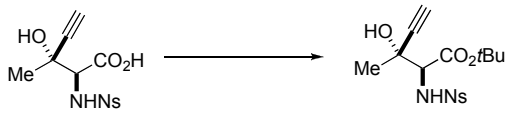
TLC $\mathbf{R_f}$ = 0.1 (5:1 chloroform/methanol)

IR (film): 3281 m, 2923 w, 1727 m, 1540 s, 1354 s, 1171 s, 1112 m, 734 m, 652 m, 595 m.

^{1}H NMR (400.1 MHz, $CDCl_3$) δ 8.08-8.06 (m, 1H), 7.92-7.90 (m, 1H), 7.74-7.72 (m, 2H), 6.42 (d, J=10 Hz, 1H), 4.17 (d, J=10 Hz, 1H), 2.48 (s, 1H), 1.62 (s, 3H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0, 147.3, 133.9, 133.8, 133.2, 130.3, 125.6, 82.6, 74.6, 74.2, 69.4, 63.6, 48.9, 27.2, 26.6.

HRMS calculated for $C_{12}H_{12}N_2O_7S$ (M+Na): 351.0263 amu, found (ESI) 351.0263 amu.



(*2S*,*3R*)-3-Hydroxy-3-methyl-2-(4-nitro-benzenesulfonyl-amino)-pent-4-ynoic acid *tert*-butyl ester. To a flame-dried 100-mL flask was added the carboxylic acid (491 mg, 1.49 mmol, 1 equiv), dichloromethane (5 mL), and cyclohexane (15 mL). Upon cyclohexane addition, the acid immediately "oiled out" of solution. Addition of *tert*-butyl trichloroacetimidate (401 μL, 2.24 mmol, 1.5 equiv) and BF_3•OEt_2 (30 μL, 0.24 mmol, 0.16 equiv) restored some of the starting material's solubility. To promote solubility, the mixture was sonicated at room temperature for 2 h. After a second aliquot of *tert*-butyl trichloroacetimidate was added (133 μL, 0.743 mmol, 0.5 equiv) and reacted over a further 30 min, the flask contents became a homongeneous mixture. This crude mixture was loaded directly to a silica gel column and purified using a stepwise mobile phase gradient of 10:1 to 5:1 to 1:1 hexanes/ethyl acetate to yield the desired *tert*-butyl ester (412 mg, 1.07 mmol, 72%).

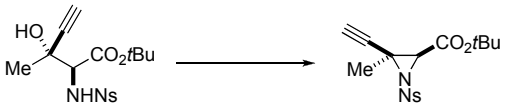
TLC R_f = 0.1 (1:1 hexanes/ethyl acetate)

IR (film): 3293 m, 2983 w, 1723 s, 1542 s, 1358 s, 1173 s, 833 m, 784 m, 737 m, 594 m.

^{1}H NMR (499.8 MHz, $CDCl_3$) δ 8.13-8.08 (m, 1H), 7.95-7.93 (m, 1H), 7.77-7.73 (m, 2H), 6.30 (d, J=9 Hz, 1H), 4.12 (d, J=9 Hz, 1H), 3.89 (s, 1H), 2.49 (s, 1H), 1.65 (s, 3H), 1.22 (s, 9H).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.0, 147.8, 134.4, 133.7, 133.0, 130.3, 125.5, 84.6, 83.3, 73.7, 69.6, 64.2, 27.6, 27.2.

HRMS calculated for $C_{16}H_{20}N_2O_7S$ (M+Na): 407.0889 amu, found (ESI) 407.0891 amu.



8

(*2S*,*3R*)-3-Ethynyl-3-methyl-1-(4-nitro-benzenesulfonyl)-aziridine-2-carboxylic acid *tert*-butyl ester (8). To a 50-mL flask containing amino-alcohol (412 mg, 1.07 mmol, 1 equiv) was added dichloromethane (10.7 mL). After cooling the reaction flask to 0 ˚C, triphenylphosphine (365 mg, 1.39 mmol, 1.3 equiv) and diisopropyl azodicarboxylate (249 mg, 1.23 mmol, 1.15 equiv) were added. The reaction was warmed to room temperature and stirred over 30 min. At this time, the solvent was removed under reduced pressure to leave behind a crude oil. This was purified by silica gel column chromatography using benzene to remove excess triphenylphosphine before eluting the desired aziridine. Elution was completed with 20:1 benzene/ethyl acetate to yield aziridine **8** (386 mg, 1.05 mmol, 99%).

TLC $\mathbf{R_f}$ = 0.1 (1:1 hexanes/ethyl acetate)

IR (film): 3279 w, 2980 w, 1733 m, 1543 s, 1358 s, 1166 s, 1121 m, 783 m, 741 m, 590 m.

^{1}H NMR (400.1 MHz, $CDCl_3$) δ 8.35-8.33 (m, 1H), 7.85-7.83 (m, 1H), 7.80-7.75 (m, 2H), 3.75 (s, 1H), 2.38 (s, 1H), 2.06 (s, 3H), 1.48 (s, 9H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.2, 134.4, 134.0, 132.9, 131.3, 124.9, 83.1, 78.8, 72.4, 52.1, 45.5, 27.9, 21.6, 19.7.

HRMS calculated for $C_{16}H_{18}N_2O_6S$ (M+Na): 389.0783 amu, found (ESI) 389.0785 amu.

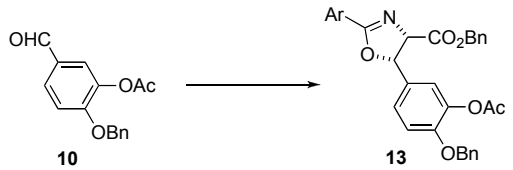
5-Benzyloxy-2-(4-methoxyphenyl)-oxazole (11). To a 500-mL flask was added Gly-O*t*Bu•TsOH (20.0 g, 59.3 mmol, 1 equiv) and a solution of saturated sodium bicarbonate (88 mL). Then dichloromethane (116 mL) and anisoyl chloride (8.6 mL, 63.4 mmol, 1.07 equiv) were added. After stirring for 1 h in a nitrogen atmosphere, the layers were separated, and the organic layer was washed with saturated sodium bicarbonate (200 mL) and 1 M HCl (200 mL). Drying the organic layer with sodium sulfate followed by concentration left 16.5 g (93%) of crude benzamide.

To an oven-dried 1000-mL flask was added the crude benzamide (16.5 g, 55.1 mmol, 1 equiv), triphenylphospine (28.9 g, 110 mmol, 2 equiv), iodine (28.0 g, 110 mmol, 2 equiv), and dichloromethane (500 mL). These were stirred until fully dissolved at which time the triethylamine was added dropwise (30.7 mL, 220 mmol, 4 equiv). The solution was stirred for 4 h before quenching with a saturated $Na_2S_2O_3$ solution (300 mL). The layers were separated and then the aqueous layer was extracted with dichloromethane (2 × 300 mL). The organics were combined and dried over anhydrous sodium sulfate before removing solvent *in vacuo* to leave ~72 g of a crude brown residue. This was purified by silica gel column chromatography using only 16.5 g silica gel and a stepwise mobile phase gradient of 20:1 to 4:1 hexanes/ethyl acetate to elute the oxazole product **11** (13.1 g, 46.6 mmol, 85%).

TLC $\mathbf{R_f}$ = 0.6 (1:1 hexanes/ethyl acetate)

^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.85 (dd, J=0.6, 9 Hz, 2H), 7.43-7.39 (m, 5H), 6.93 (dd, J=0.6, 9 Hz, 2H), 6.19 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.7, 159.1, 152.9, 134.8, 128.8, 128.7, 128.0, 126.9, 120.4, 114.1, 101.4, 74.0, 55.3.



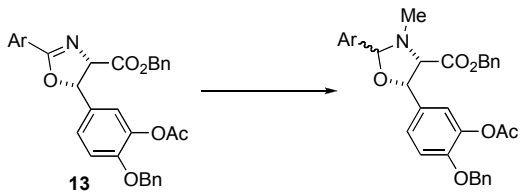
(*4S*,*5S*)-5-(3-Acetoxy-4-benzyloxyphenyl)-2-(4-meth-oxyphenyl)-4,5-dihydrooxazole-4-(carboxylic acid benzyl ester) (13). Molecular sieves (3Å, 58.4 mg, dried overnight in a 300 °C oven), anhydrous sodium sulfate (3.5 mg, 0.0246 mmol, 0.2 equiv), 5-methoxy-2-(4-methoxyphenyl)-oxazole **11** (34.7 mg, 0.123 mmol, 1 equiv), benzaldehyde **10** (40.0 mg, 0.148 mmol, 1.2 equiv), and (*R*)-2,2'-bis(3,5-di-*tert*-butyl-2-hydroxybenzilideneamino)-1,1'-binaphthyl aluminum chloride **12** (9.1 mg, 0.0123 mmol, 0.1 equiv) were added to an argon-purged flame-dried flask. The preparation of benzaldehyde **10** and the Salen catalyst have been previously described.[2,3] After purging with argon, silver hexafluoroantimonate (very hygroscopic!) (4.6 mg, 0.0135 mmol, 0.11 equiv) was added quickly followed again by an argon purge. Toluene (200 μL) was added and the reaction was wrapped in aluminum foil and stirred at room temperature for 25 h in a closed environment. The reaction mixture was loaded directly onto a short silica gel column and all compounds were eluted using ethyl acetate. The crude material was further purified using a second silica gel column. The Salen ligand (*R*)-2,2'-bis(3,5-di-*tert*-butyl-2-hydorxybenzilideneamino)-1,1'-binaphthyl was eluted using 9:1 hexanes/ethyl acetate, followed by 3-acetoxy-4-benzyloxybenzldehyde which eluted with 6:1 hexanes/ethyl acetate. Continuing the elution with 5:1 to 1:1 hexanes/ethyl acetate provided *cis*-oxazoline **13** (64.9 mg, 0.118 mmol, 96%). Enantioselectivity was determined to be 98% *ee* by HPLC using a Chiralpak AD column. The major isomer eluted at 22.73 min and the minor isomer eluted at 29.20 min with 50% isopropyl alcohol in hexanes.

TLC $\mathbf{R_f}$ = 0.5 (1:1 hexanes/ethyl acetate)

^{1}H NMR (499.8 MHz, $CDCl_3$) δ 8.00 (dt, J=2.5, 7 Hz, 2H), 7.42-7.29 (m, 8H), 7.15-7.08 (m, 3H), 7.06 (d, J=1 Hz, 1H), 6.98 (dt, J=2.5, 7 Hz, 2H), 6.88 (d, J=10 Hz, 1H), 5.84 (d, J=11 Hz, 1H), 5.28 (d, J=11 Hz, 1H), 5.09 (s, 2H), 4.86 (d, J=10 Hz, 1H), 4.55 (d, J=10 Hz, 1H), 3.90 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.2, 168.7, 166.4, 162.7, 150.4, 140.0, 136.3, 135.1, 130.6, 128.8, 128.6, 128.5, 128.3, 128.1, 128.0, 127.0, 125.1, 121.1, 119.1, 113.8, 113.4, 82.1, 73.6, 70.4, 66.9, 55.4, 20.5.

MS calculated for $C_{33}H_{29}NO_7$ (M+H): 552.3 amu, found (ESI): 552.1 amu.

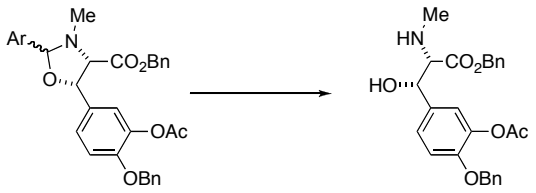


(*4S*,*5S*)-5-(3-Acetoxy-4-benzyloxyphenyl)-2-(4-meth-oxyphenyl)-3-methyl-oxazolidine-4-carboxylic acid benzyl ester. *Cis*-oxazoline **13** (9.7 g, 17.6 mmol, 1 equiv) was dissolved in dichloromethane (180 mL) at ambient temperature. Methyl trifluoromethanesulfonate (freshly distilled over calcium hydride, 3.0 mL, 26.4 mmol, 1.5 equiv) was added and the reaction was stirred for 2 h. The volatiles were then removed under reduced pressure before resuspending the residue in dichloromethane (180 mL) at 0 °C. An ice cold saturated sodium bicarbonate solution (180 mL) and sodium borohydride (1.33 g, 35.2 mmol, 2 equiv) were added all at once with vigorous stirring. Hydrogen gas evolved and the reaction was stirred for 15 min before separating the two layers. The aqueous layer was extracted with dichloromethane (3 × 180 mL) and the combined organic layer extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave 10.3 g of crude material for purification. Recrystallization using a mixture of hexanes and ethyl acetate yielded 6.3 g of shiny white crystals of the desired *cis*-oxazolidine. The mother liquor was concentrated under reduced pressure and the residue purified by flash silica gel chromatography using 6:1 hexanes/ethyl acetate to furnish an additional 0.9 g of the desired *cis*-oxazolidine (total: 7.2 g, 12.7 mmol, 72%).

TLC R_f = 0.65 (1:1 hexanes/ethyl acetate)

^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.61 (7.46) (d, J=12 Hz, 2H), 7.40-7.08 (m, 9H), 6.94 (6.92) (d, J=12 Hz, 2H), 6.87 (d, J=8 Hz, 1H), 5.27 (5.64) (d, J=9 Hz, 1H), 5.07 (5.05) (s, 2H), 4.84 (4.85) (d, J=12 Hz, 1H), 4.81 (5.80) (s, 1H), 4.57 (4.60) (d, J=12 Hz, 1H), 3.83 (3.82) (s, 3H), 3.78 (3.26) (d, J=9 Hz, 1H), 2.32 (2.38) (s, 3H), 2.27 (s, 3H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.4, 168.7 (168.8), 160.5, 150.1, 139.8 (140.0), 136.6, 135.3, 131.1, 129.8, 129.2, 129.0, 128.6, 128.5 (128.5), 128.3, 128.1, 127.9, 127.1, 126.2, 124.7, 122.2, 120.9, 119.1, 113.8 (113.8), 113.2 (113.3), 98.4 (98.3) 79.2, 71.6, 70.4, 66.7, 55.3, 36.8, 33.0, 29.7, 20.6. The NMR chemical shifts in parentheses are the shifts for the minor diastereomer.



(*4S*,*5S*)-3-(3-Acetoxy-4-benzyloxyphenyl)-3-hydroxy-2-methylaminopropionic acid benzyl ester. The *cis*-oxazolidine starting material (6.8 g, 12.0 mmol, 1 equiv) was dissolved in THF (300 mL) at which time an oxalic acid solution (0.1 N, 300 mL, 29.9 mmol, 2.5 equiv) was added. The reaction mixture was stirred for 24 h before diluting with dichloromethane (200 mL). The layers were separated then the aqueous layers was extracted with dichloromethane (6 × 200 mL). The organics were combined and then washed with brine (2 × 300 mL). The aqueous washes were combined and then extracted further with 1:3 methanol/dichloromethane (6 × 250 mL) before basifying the aqueous layer with sodium carbonate. The aqueous layer was extracted one last time with dichloromethane (4 × 250 mL). The collected organic extracts were combined and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude white solid (~10 g) was purified using silica gel column chromatography. 4-Methoxybenzaldehyde was eluted with 4:1 then 2:1 hexanes/ethyl acetate. The desired amino-alcohol (5.4 g, 12.0 mmol, 99%) eluted with 10:1 to 5:1 chloroform/methanol.

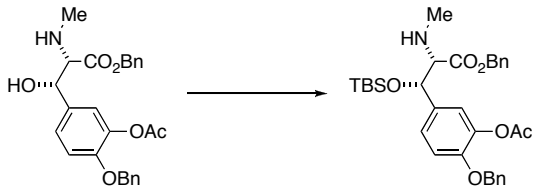
TLC R_f = 0.1 (1:2 hexanes/ethyl acetate)

IR (film): 3367 m, 2925 m, 1739 s, 1509 s, 1453 m, 1270 m, 1198 s, 1114 m, 1072 s, 1015 s.

^{1}H NMR (499.8 MHz, $CDCl_3$) δ 7.38-7.31 (m, 8H), 6.98 (d, J=2 Hz, 1H), 6.95 (dd, J=2, 8 Hz, 1H), 6.84 (d, J=8 Hz, 1H), 5.07 (d, J=12 Hz, 1H), 5.03 (s, 2H), 5.03 (d, J=12 Hz, 1H), 4.99 (d, J=5 Hz, 1H), 3.59 (d, J=5 Hz, 1H), 2.43 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.4, 168.9, 149.8, 140.0, 136.6, 135.0, 132.8, 128.5, 128.4, 127.9, 127.1, 124.2, 120.6, 113.6, 71.9, 70.6, 68.5, 66.9, 35.0, 20.6.

HRMS calculated for $C_{26}H_{27}NO_6$ (M+Na): 472.1736 amu, found (ESI) 472.1737 amu.



(*4S*,*5S*)-3-(3-Acetoxy-4-benzyloxyphenyl)-2-methylamino-3-*tert*-butyldimethylsilyl-oxypropionic acid benzyl ester. To an evacuated 1000-mL flask containing the amino alcohol (5.7 g, 12.7 mmol, 1 equiv) was added dichloromethane (127 mL) and 2,6-lutidine (2.95 mL, 25.4 mmol, 2 equiv). The solution was cooled to 0 ˚C at which time TBSOTf was added dropwise (4.4 mL, 19.1 mmol, 1.5 equiv). After 30 min, a peach color had developed and at 90 min, more 2,6-lutidine (1.5 mL, 12.7 mmol, 1 equiv) and TBSOTf (583 μL, 3.54 mmol, 0.2 equiv) were added to bring the reaction to completion as monitored by TLC. After 30 min, the reaction was quenched with pH 2.5 phosphate buffer (100 mL) at 0 ˚C. The layers were separated and the aqueous layer was extracted with dichloromethane (6 × 100 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to leave 10.7 g of a crude brown oil. This was purified by silica gel chromatography by eluting trace quantities of the bis-silylated product with 5:1 hexanes/ethyl acetate. The desired *mono*-silylated product was eluted using 2:1 to 1:1 hexanes/ethyl acetate (6.7 g, 11.9 mmol, 87%).

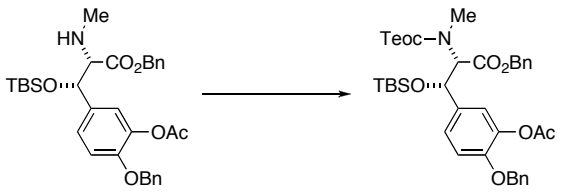
TLC R_f = 0.7 (1:2 hexanes/ethyl acetate)

IR (film): 2930 w, 2856 w, 1768 m, 1736 m, 1509 m, 1260 m, 1198 s, 1089 m, 1010 w, 838 m, 779 m, 736 w, 697 m.

^{1}H NMR (499.8 MHz, $CDCl_3$) δ 7.40-7.29 (m, 9H), 7.07 (dd, J=2, 8 Hz, 1H), 7.04 (d, J=2 Hz, 1H), 6.90 (d, J=8 Hz, 1H), 5.18 (d, J=12 Hz, 1H), 5.05 (s, 2H), 5.05 (d, J=12 Hz, 1H), 4.76 (d, J=7 Hz, 1H), 3.36 (d, J=7 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 0.84 (s, 3H), 0.0 (s, 9H), -0.22 (s, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.9, 168.8, 149.8, 140.0, 136.7, 135.7, 134.6, 128.5, 128.5, 128.4, 128.2, 127.9, 127.2, 125.0, 121.3, 113.3, 75.7, 70.9, 70.6, 66.4, 34.9, 25.7, 20.6, 18.0, -4.6, -5.3.

HRMS calculated for $C_{32}H_{41}NO_6Si$ (M+Na): 586.2601 amu, found (ESI) 586.2604 amu.



(*4S*,*5S*)-3-(3-Acetoxy-4-benzyloxyphenyl)-2-[2-(trimethylsilyl)-ethoxycarbonylmethylamino]-3-*tert*-butyldimethylsilyl-oxypropionic acid benzyl ester. The secondary amine (4.9 g, 8.69 mmol, 1 equiv) was dissolved in acetonitrile (87 mL, 0.1 M) and sodium carbonate (1.83 g, 21.7 mmol, 2.5 equiv) and Teoc-Cl (0.470 M solution in toluene, 37.0 mL, 17.4 mmol, 2 equiv) were added. Teoc-Cl was prepared according to literature methods.[4] After stirring for 1 h at room temperature under an atmosphere of nitrogen, the reaction was diluted with dichloromethane (100 mL) and quenched with pH 2.5 phosphate buffer (100 mL). The phases were separated, the aqueous layer was extracted with dichloromethane (2 × 100 mL), and the organic extracts were combined and dried with anhydrous sodium sulfate. After removing the solvent under reduced pressure, the crude material was purified by silica gel chromatography using a stepwise mobile phase gradient of 20:1 to 8:1 hexanes/ethyl acetate to yield 6.0 g (98%) protected amine.

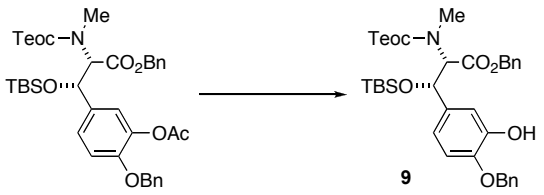
TLC R_f = 0.68 (2:1 hexanes/ethyl acetate)

IR (film): 2954 m, 2857 w, 2360 m, 2341 w, 1701 s, 1510 m, 1251 s, 1197 s, 1121 m, 1079 m, 838 s, 779 m, 696 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 7.41-7.29 (m, 10H), 7.14 (dd, J=2, 9 Hz, 1H), 7.11 (d, J=8 Hz, 1H), 7.09 (d, J=2 Hz, 1H), 5.19 (s, 2H), 5.16 (d, J=9 Hz, 1H), 5.09 (s, 2H), 4.75 (d, J=9 Hz, 1H), 3.98-3.88 (m, 2H), 2.68 (s, 3H), 2.19 (s, 3H), 0.83-0.79 (m, 2H), 0.78 (s, 9H), 0.0 (s, 3H), -0.02 (s, 9H), -0.22 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C) δ 168.4, 167.3, 149.3, 139.5, 136.4, 135.3, 133.0, 127.7, 127.7, 127.4, 127.3, 127.1, 126.5, 124.9, 121.2, 113.7, 71.8, 70.1, 65.5, 64.1, 62.6, 31.2, 25.0, 19.5, 17.0, 16.7, -2.2, -5.3, -5.8.

HRMS calculated for $C_{38}H_{53}NO_8Si_2$ (M+Na): 730.3207 amu, found (ESI) 730.3203 amu.



(*4S*,*5S*)-2-[2-(trimethylsilyl)-ethoxycarbonylamino]-3-(3-benzyloxy-4-hydroxyphenyl)-3-(*tert*-butyldimethylsilyloxy)propionic acid benzyl ester (9). Fully protected Tyr residue (545.3 mg, 0.770 mmol, 1 equiv) was dissolved in THF (7.7 mL) and then cooled to 0 ˚C. At this time, hydrazine hydrate was added dropwise (74.7 μL, 1.54 mmol, 2 equiv), turning the colorless solution brown. Some precipitate crashed out of solution after 2 h and the reaction was complete after 3 h. After diluting the mixture with ethyl acetate (8 mL), pH 2.5 phosphate buffer (8 mL) was added to quench the excess reagent. The layers were then separated and the aqueous layer was extracted with ethyl acetate (3 × 8 mL). The organics were combined and dried over anhydrous sodium sulfate before removing the solvent under reduced pressure to leave 517 mg of a crude oil. This residue was purified using silica gel column chromatography and a stepwise mobile phase gradient of 20:1 to 10:1 hexanes/ethyl acetate to elute the desired phenol **9** (500.4 mg, 0.751, 98%).

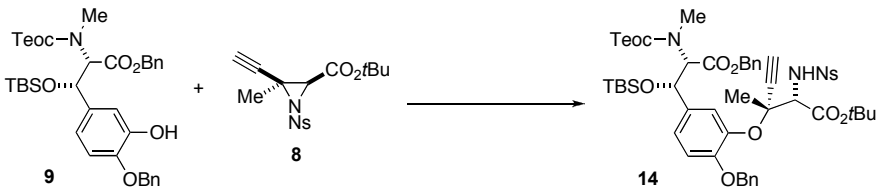
TLC $\mathbf{R}_f$ = 0.9 (50:1 chloroform/methanol)

IR (film): 3385 w, 2954 m, 2857 w, 1740 m, 1700 s, 1508 m, 1456 m, 1252 s, 1175 s, 1078 m, 838 s, 779 m, 696 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 7.46-7.44 (m, 2H), 7.39-7.28 (m, 8H), 6.88 (d, J=8 Hz, 1H), 6.86 (d, J=2 Hz, 1H), 6.70 (dd, J=2, 8 Hz, 1H), 5.20 (d, J=13 Hz, 1H), 5.16 (s, J=13 Hz, 1H), 5.07 (s, 2H), 5.04 (d, J=9 Hz, 1H), 4.74 (d, J=9 Hz, 1H), 3.99-3.87 (m, 2H), 2.68 (s, 3H), 0.85-0.79 (m, 2H), 0.78 (s, 9H), -0.01 (s, 3H), -0.02 (s, 9H), -0.22 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C) δ 168.6, 146.4, 146.1, 136.9, 135.3, 133.2, 127.8, 127.6, 127.4, 127.2, 127.0, 117.7, 114.6, 114.0, 72.2, 70.3, 65.4, 64.0, 62.5, 31.0, 25.0, 17.0, 16.7, -2.1, -5.3, -5.8.

HRMS calculated for $C_{36}H_{51}NO_7Si_2$ (M+Na): 688.3102 amu, found (ESI) 699.3099 amu.



(*2S*,*3S*,*1'S*,*2'S*)-3-[2-Benzyloxy-5-(2-benzyloxycarbonyl-1-(*tert*-butyl-dimethyl-silanyloxy)-2-{methyl-[2-(trimethyl-silanyl)-ethoxycarbonyl]-amino}-ethyl)-phenoxy]-3-methyl-2-(2-nitro-benzenesulfonylamino)-pent-4-ynoic acid *tert*-butyl ester (14). Toluene (2.5 mL, 0.2 M) was added to a flask containing phenol **9** (334.4 mg, 0.502 mmol, 1 equiv) and aziridine **8** (369.9 mg, 1.01 mmol, 1.99 equiv). The solution was cooled to 0 ˚C and copper(I) acetate (0.6 mg, 0.005 mmol, 0.01 equiv.) was added dropwise as a 0.1 M toluene solution followed by DBU (purified by reduced pressure distillation, 167 μL, 1.12 mmol, 2.2 equiv). The reaction was stirred at 0-4 ˚C in a nitrogen atmosphere for 13 d until the aziridine was consumed as confirmed by TLC. The solvent was then removed by concentration; the crude foam was purified by silica gel chromatography using a stepwise mobile phase gradient of 20:1 to 5:1 hexanes/ethyl acetate to yield 452.0 mg (87%) of the desired ether.

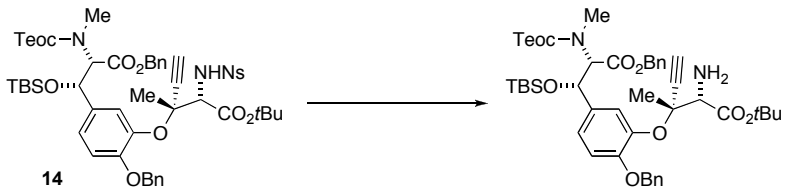
TLC R_f = 0.61 (3:2 hexanes/ethyl acetate)

IR (film): 2954 w, 1739 m, 1699 m, 1543 m, 1360 m, 1252 s, 1173 s, 839 s, 780 m, 738 m, 697 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 8.08-8.06 (m, 1H), 7.96-7.79 (m, 3H), 7.54 (d, J=9 Hz, 1H), 7.46-7.43 (m, 2H), 7.37-7.289 (m, 6H), 7.27 (d, J=2 Hz, 1H), 7.17-7.10 (m, 1H), 7.04 (dd, J=2, 8 Hz, 1H), 7.00 (d, J=8 Hz, 1H), 5.20 (d, J=9 Hz, 1H), 5.17 (d, J=9 Hz, 1H), 5.10 (d, J=9 Hz, 1H), 5.10 (s, 2H), 4.70 (d, J=9 Hz, 1H), 4.29 (d, J=10 Hz, 1H) 3.98-3.85 (m, 2H), 3.38 (s, 1H), 2.68 (s, 3H), 1.61 (s, 3H), 1.24 (s, 9H), 0.86-0.76 (m, 2H), 0.78 (s, 9H), 0.0 (s, 3H), -0.04 (s, 9H), -0.2 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C) δ 168.5, 165.5, 151.4, 147.0, 142.9, 136.6, 135.3, 133.7, 132.9, 132.7, 132.1, 127.8, 127.6, 127.5, 127.3, 127.0, 126.8, 123.3, 122.5, 114.1, 81.5, 79.4, 77.6, 72.0, 70.1, 65.5, 64.2, 63.7, 62.6, 31.4, 26.9, 25.0, 23.7, 17.0, 16.7, -2.1, -5.2, -5.8.

HRMS calculated for $C_{52}H_{69}N_3O_{13}SSi_2$ (M+Na): 1054.3987 amu, found (ESI) 1054.3981 amu.



(*2S*,*3S*,*1'S*,*2'S*)-2-Amino-3-[2-benzyloxy-5-(2-benzyloxycarbonyl-1-(*tert*-butyl-dimethyl-silanyloxy)-2-{methyl-[2-(trimethyl-silanyl)-ethoxycarbonyl]-amino}-ethyl)-phenoxy]-3-methyl-pent-4-ynoic acid *tert*-butyl ester. Cesium carbonate (211.5 mg, 0.649 mmol, 1.5 equiv) was added to the nosyl-protected amine **14** (446.8 mg, 0.433 mmol, 1 equiv) and the mixture was dissolved in DMF (4.3 mL, 0.1 M). Thiophenol (111.1 µL, 1.08 mmol, 2.5 equiv) was added dropwise and the reaction stirred at room temperature in a nitrogen atmosphere for 2 h. Then the reaction was diluted with ether (15 mL) and quenched with a saturated solution of sodium bicarbonate (15 mL). The phases were separated, the aqueous layer was extracted with ether (2 × 15 mL), and the organic extracts were combined, dried with anhydrous sodium sulfate, and concentrated. The crude material was purified by silica gel chromatography using a stepwise mobile phase gradient of 30:1 to 10:1 benzene/ethyl acetate to yield 336.8 mg (92%) of the primary amine.

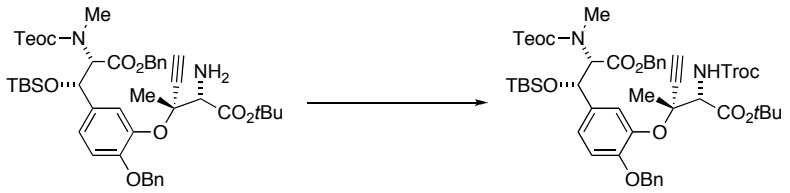
TLC R_f = 0.48 (5:1 benzene/ethyl acetate)

IR (film): 2954 m, 2856 m, 1734 s, 1702 s, 1506 m, 1456 m, 1252 s, 1174 s, 1074 m, 839 s, 779 m, 697 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 7.46-7.41 (m, 3H), 7.39-7.29 (m, 7H), 7.05-7.01 (m, 3H), 5.21 (d, J=13 Hz, 1H), 5.17 (d, J=13 Hz, 1H), 5.11 (d, J=9 Hz, 1H), 5.07 (s, 2H), 4.73 (d, J=9 Hz, 1H), 3.99-3.90 (m, 2H), 3.61 (s, 1H), 2.69 (s, 3H), 1.50 (s, 3H), 1.44 (s, 9H), 0.83-0.74 (m, 2H), 0.79 (s, 9H), 0.01 (s, 3H), -0.03 (s, 9H), -0.20 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C) δ 169.6, 168.5, 151.3, 143.5, 136.6, 135.3, 132.6, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 122.7, 121.9, 114.1, 82.8, 80.0, 78.2, 72.0, 70.3, 65.5, 64.2, 62.8, 62.6, 31.3, 27.2, 25.0, 21.5, 17.0, 16.8, -2.2, -5.3, -5.8.

HRMS calculated for $C_{46}H_{66}N_2O_9Si_2$ (M+H): 847.4385 amu, found (ESI) 847.4835 amu.



(*2S*,*3S*,*1'S*,*2'S*)-3-[2-Benzyloxy-5-(2-benzyloxycarbonyl-1-(*tert*-butyl-dimethyl-silanyloxy)-2-{methyl-[2-(trimethyl-silanyl)-ethoxycarbonyl]-amino}-ethyl)-phenoxy]-3-methyl-2-(2,2,2-trichloro-ethoxycarbonylamino)-pent-4-ynoic acid *tert*-butyl ester. Sodium bicarbonate (906.6 mg, 10.8 mmol, 2 equiv) was added to the primary amine (4.5681 g, 5.39 mmol, 1 equiv) followed by THF (54 mL, 0.1 M) and 2,2,2-trichloroethyl chloroformate (1.27 mL, 9.17 mmol, 1.7 equiv). After stirring the reaction at room temperature in an atmosphere of nitrogen for 35 min, the reaction was diluted with dichloromethane (50 mL) and quenched with pH 2.5 phosphate buffer (50 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 × 50 mL), and the organic extracts were combined, dried with sodium sulfate, and concentrated. The crude material was then purified by silica gel chromatography using a stepwise mobile phase gradient of 30:1 to 10:1 hexanes/ethyl acetate to yield 5.2869 g (96%) of the Troc protected amine.

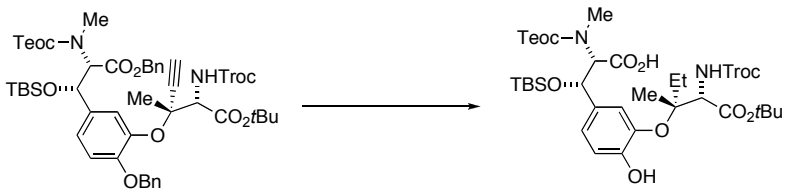
TLC $\mathbf{R}_f$ = 0.72 (2:1 hexane/ethyl acetate)

IR (film): 3309 w, 2954 m, 2857 w, 1742 s, 1702 m, 1506 m, 1251 s, 1173 m, 1128 m, 1097 m, 838 s, 780 m, 734 m, 697 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 7.46-7.45 (m, 2H), 7.39-7.33 (m, 7H), 7.31-7.27 (m, 2H), 7.03 (dd, J=2, 9 Hz, 1H), 6.99 (d, J=9 Hz, 1H), 5.20 (d, J=13 Hz, 1H), 5.18 (d, J=13 Hz, 1H) 5.15 (s, 2H), 5.10 (d, J=9 Hz, 1H), 4.81 (d, J=12 Hz, 1H), 4.76 (d, J=12 Hz, 1H), 4.70 (d, J=9 Hz, 1H), 3.98-3.89 (m, 2H), 3.34 (s, 1H), 2.67 (s, 3H), 1.69 (s, 3H), 1.45 (s, 9H), 0.82-0.76 (m, 2H), 0.78 (s, 9H), 0.0 (s, 3H), -0.03 (s, 9H), -0.21 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C) δ 168.5, 166.2, 151.3, 143.2, 135.3, 132.7, 127.7, 127.6, 127.4, 127.3, 127.0, 126.8, 123.3, 122.2, 114.0, 95.5, 81.2, 81.1, 78.9, 77.3, 73.6, 72.0, 70.1, 65.5, 64.2, 62.6, 62.3, 31.3, 27.2, 25.0, 23.9, 21.5, 17.0, 16.7, -2.1, -5.8.

HRMS calculated for $C_{49}H_{67}Cl_3N_2O_{11}Si_2$ (M+Na): 1043.3247 amu, found (ESI) 1043.3236 amu.



(*2S*,*3R*,*1'S*,*2'S*)-3-[5-(1-(*tert*-Butyl-dimethyl-silanyloxy)-2-carboxy-2-{methyl-[2-(trimethyl-silanyl)-ethoxycarbonyl]-amino}-ethyl)-2-hydroxy-phenoxy]-3-methyl-2-(2,2,2-trichloro-ethoxycarbonylamino)-pentanoic acid *tert*-butyl ester. To a 25 mL-flask containing the alkyne (495 mg, 0.484 mmol, 1 equiv) was added 20% $Pd(OH)_2/C$ (48 mg, 20% by mass) and ethyl acetate (4.8 mL). The mixture was then placed under a 1 atm hydrogen environment and stirred at room temperature for 4 d, checking aliquots periodically by ^1H NMR to monitor reaction progress. The reaction contents were then filtered over Celite and washed copiously with ethyl acetate. Solvent was removed under reduced pressure to furnish the desired hydrogenated product (406 mg, 0.480 mmol, 99%). ^1H NMR analysis showed it to be a single product that did not require further purification.

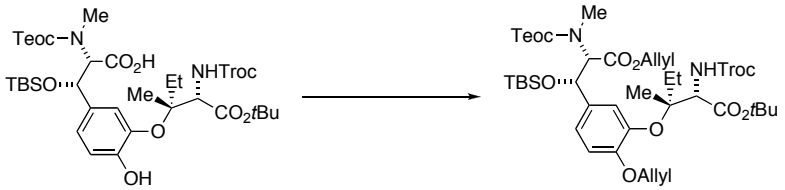
TLC $\mathbf{R_f}$ = 0.51 (2:1 hexane/ethyl acetate)

IR (film): 3424 br m, 2958 m, 1722 s, 1509 m, 1259 s, 1153 s, 1098 s, 840 s, 807 s, 730 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 8.90 (br, s, 5H), 7.65 (br, s, 1H), 6.93-6.91 (m, 2H), 6.81-6.77 (m, 1H), 5.00 (d, J=9 Hz, 1H), 4.86 (d, J=13 Hz, 1H), 4.82 (d, J=13 Hz, 1H), 4.62 (d, J=9 Hz, 1H), 4.29 (d, J=8 Hz, 1H), 4.00-3.86 (m, 2H), 2.69 (s, 3H), 1.94-1.88 (m, 1H), 1.64-1.55 (m, 1H), 1.47 (s, 9H), 1.35 (s, 3H), 0.91 (t, J=7 Hz, 3H), 0.81-0.78 (m, 2H), 0.81 (s, 9H), 0.03 (s, 3H), -0.01 (s, 9H), -0.19 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C): δ 170.6, 168.1, 155.0, 154.0, 150.0, 149.7, 140.5, 132.3, 122.5, 122.1, 115.2, 95.7, 83.3, 80.9, 73.5, 70.4, 67.7, 63.5, 62.3, 61.5, 60.4, 31.3, 30.9, 29.0, 27.2, 27.1, 27.0, 25.2, 25.0, 20.5, 20.1, 17.1, 16.9, 7.5, -2.2, -3.8, -5.3, -5.8.

HRMS calculated for $C_{35}H_{59}Cl_3N_2O_{11}Si_2$ (M+Na): 867.2621 amu, found (ESI) 867.2626 amu.



(*2S*,*3R*,*1'S*,*2'S*)-3-[2-Allyloxy-5-(2-allyloxycarbonyl-1-(*tert*-butyl-dimethyl-silanyloxy)-2-{methyl-[2-(trimethyl-silanyl)-ethoxycarbonyl]-amino}-ethyl)-phenoxy]-3-methyl-2-(2,2,2-trichloro-ethoxycarbonylamino)-pentanoic acid *tert*-butyl ester. To a 25-mL flask was added the free acid (406 mg, 0.479 mmol, 1 equiv) and DMF (4.8 mL). When DBU was added (199 μL, 1.44 mmol, 3 equiv), the color immediately turned dark red. Lastly, allyl bromide (166 μL, 1.92 mmol, 4 equiv) was added and the mixture was stirred at room temperature for 3 h. At this time additional aliquots of allyl bromide (120 μL, 1.39 mmol, 2.9 equiv) and DBU (100 μL, 0.721 mmol, 1.5 equiv) were added and the solution was stirred 2 h longer. The reaction was then diluted with diethyl ether (15 mL) before quenching with pH 2.5 phosphate buffer (15 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The organics were combined, dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* to leave a crude oil. The crude material was purified by silica gel column chromatography using a stepwise mobile phase gradient of 30:1 to 10:1 hexanes/ethyl acetate to yield the desired bis-allylated product (309 mg, 0.334 mmol, 70%).

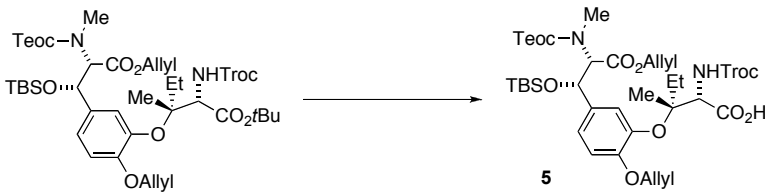
TLC R_f = 0.76 (2:1 hexane/ethyl acetate)

IR (film): 3384 br m, 2960 m, 2858 m, 1742 s, 1704 m, 1504 m, 1260 s, 1093 s, 839 m, 803 s, 733 m, 704 m, 596 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 7.08-7.06 (m, 2H), 7.03 (d, J=2 Hz, 1H), 6.15-6.06 (m, 1H), 5.99-5.91 (m, 1H), 5.42-5.30 (m, 2H), 5.29-5.22 (m, 2H), 5.08 (d, J=9 Hz, 1H), 4.85 (d, J=12 Hz, 1H), 4.81 (d, J=12 Hz, 1H), 4.73 (d, J=9 Hz, 1H), 4.65-4.63 (m, 4H), 4.29 (d, J=8 Hz, 1H), 3.98-3.86 (m, 2H), 2.73 (s, 3H), 1.87-1.78 (m, 1H), 1.60-1.51 (m, 1H), 147 (s, 9H), 1.33 (s, 3H), 0.94 (t, J=7 Hz, 3H), 0.84-0.77 (m, 2H), 0.80 (s, 9H), 0.03 (s, 3H), -0.02 (s, 9H), -0.20 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C): δ 168.3, 168.0, 151.5, 142.3, 132.8, 131.7, 122.9, 122.8, 117.5, 113.1, 95.6, 83.4, 80.8, 73.6, 71.8, 69.0, 64.3, 63.8, 62.6, 60.1, 30.9, 28.7, 27.2, 27.1, 25.0, 24.9, 17.0, 16.7, 7.4, -2.2, -5.3, -5.8.

HRMS calculated for $C_{41}H_{67}Cl_3N_2O_{11}Si_2$ (M+Na): 947.3247 amu, found (ESI) 947.3254 amu.



(*2S*,*3R*,*1'S*,*2'S*)-3-[2-Allyloxy-5-(2-allyloxycarbonyl-1-(*tert*-butyl-dimethyl-silanyloxy)-2-{methyl-[2-(trimethyl-silanyl)-ethoxycarbonyl]-amino}-ethyl)-phenoxy]-3-methyl-2-(2,2,2-trichloro-ethoxycarbonylamino)-pentanoic acid (5). To an oven-dried and dessicator-cooled 50-mL sealed tube was added silica gel (10.3 g, 5 g/mmol). The *tert*-butyl ester (1.9128 g, 2.06 mmol, 1 equiv) was dissolved in toluene and added to the vessel, followed by enough toluene to bring the reaction to its final volume (20.6 mL, 0.1 M). The vessel was closed with a Teflon screw top and stirred in a 90 ˚C oil bath for 22 h. After allowing the reaction mixture to cool, it was then concentrated under reduced pressure to remove solvent and leave a tan powder. The acid was purified by silica gel chromatography by loading the crude powder directly onto the column and using a mobile phase gradient of 5:1 hexanes/ethyl acetate to 10:1 chloroform/methanol. This separated the product acid from unreacted starting material. The remaining *tert*-butyl ester (451.5 mg, 0.49 mmol, 1 equiv) was exposed to the reaction conditions again (2.4 g silica gel at 5 g/mmol and 4.9 mL toluene at 0.1 M). A 15 h reaction and identical purification steps gave a total yield of 1.1794 g of acid **5** which was carried through to the next step.

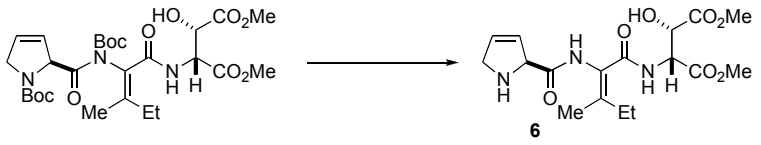
TLC $\mathbf{R_f}$ = 0.38 (10:1 chloroform/methanol)

IR (film): 3333 br w, 3054 m, 2959 m, 2857 m, 2306 w, 1739 m, 1503 m, 1264 s, 1093 m, 807 m, 739 s.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 7.05 (dd, J=2, 8 Hz, 1H), 6.97-6.93 (m, 2H), 6.09-6.01 (m, 1H), 5.99-5.90 (m, 1H), 5.39-5.30 (m, 2H), 5.26-5.22 (m, 2H), 5.06 (d, J=9 Hz, 1H), 4.73 (d, J=9 Hz, 1H), 4.70-4.61 (m, 4H), 4.52 (d, J=5 Hz, 1H), 3.99-3.87 (m, 2H), 3.86 (d, J=11 Hz, 1H), 3.80 (d, J=11 Hz, 1H), 2.72 (s, 3H), 1.93-1.85 (m, 1H), 1.73-1.65 (m, 1H), 1.36 (s, 3H), 0.88 (t, J=7 Hz, 3H), 0.84-0.80 (m, 2H), 0.80 (s, 9H), 0.02 (s, 3H), -0.01 (s, 9H), -0.21 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C): δ 168.5, 146.3, 145.9, 133.6, 133.0, 131.8, 117.7, 117.4, 116.3, 114.5, 113.6, 75.1, 72.2, 69.2, 64.2, 63.8, 62.5, 30.8, 25.2, 25.0, 17.0, 16.7, -2.1, -5.3, -5.8.

HRMS calculated for $C_{37}H_{59}Cl_3N_2O_{11}Si_2$ (M+Na): 891.2621 amu, found (ESI) 891.2623 amu.



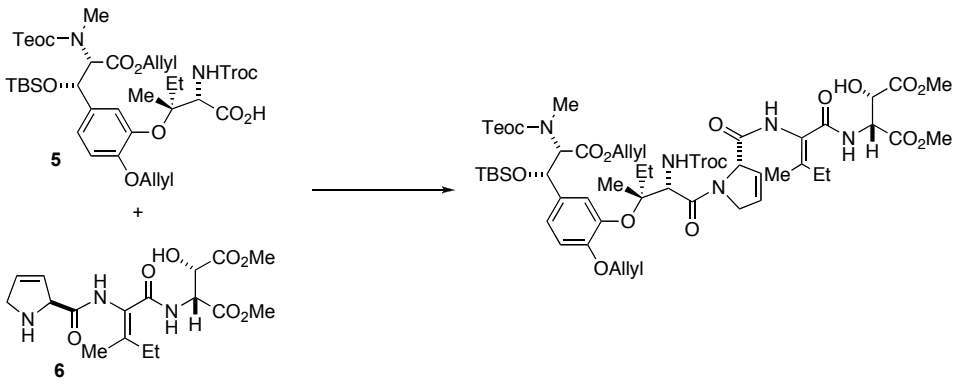
6

(*2R*,*3S*)-2-{(*E*)-[((*S*)-2,5-Dihydro-1*H*-pyrrole-2-carbonyl)-amino]-3-methyl-pent-2-enoylamino}-3-hydroxy-succinic acid dimethyl ester (6). The fully protected side-chain tripeptide (1.2233 g, 2.10 mmol, 1 equiv) was dissolved in dichloromethane (16.8 mL), cooled to 0 ˚C, and trifluoroacetic acid (4.2 mL, 20% solution, 0.1 M) was added dropwise. After stirring for 14 h at 0-4 ˚C in a nitrogen atmosphere, the reaction was concentrated under reduced pressure. The crude material was treated to the reaction conditions for a second time. After 21 h, the reaction was concentrated under reduced pressure to remove the solvent and trifluoroacetic acid and leave a crude brown residue. This material was purified by silica gel chromatography using a stepwise mobile phase gradient of 30:1 to 20:1 ethyl acetate/methanol with 1% triethylamine to yield 1.1278 g of the amine which was taken directly into the next step. The preparation of the starting material is described elsewhere.[5]

TLC R_f = 0.15 (10:1 chloroform/methanol)

IR (film): 3424 br m, 2992 m, 2703 br m, 2505 br w, 1752 m, 1679 s, 1477 m, 1203 s, 1131 s, 831 m, 800 m, 721 m.

HRMS calculated for $C_{17}H_{25}N_3O_7$ (M+Na): 406.1590 amu, found (ESI) 406.1596 amu.



Compound 27. To a flask containing acid **5** (1.1409 g, 1.31 mmol, 1 equiv), amine **6** (1.1211 g, 1 equiv based upon 2.1 mmol-scale reactions to make the acid and amine) was added as a solution in acetonitrile. More acetonitrile was added to bring the solution to its final volume (13.1 mL, 0.1 M). Then PyBOP (1.36 g, 2.62 mmol, 2 equiv) and *N*,*N*-diisopropylethylamine (867 μL, 5.24 mmol, 4 equiv) were added; after 2 h, a further 2 equiv of PyBOP and 4 equiv of base were added. After stirring the reaction at room temperature in a nitrogen atmosphere for a total of 23 h, the solution was diluted with dichloromethane (75 mL) and quenched with 1 M HCl (75 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (2 × 75 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The crude material was purified by silica gel chromatography using a stepwise mobile phase gradient of 4:1 to 1:1 hexanes/ethyl acetate to yield 719.2 mg (28% over two steps from the *tert*-butyl ester) of the desired pentapeptide.

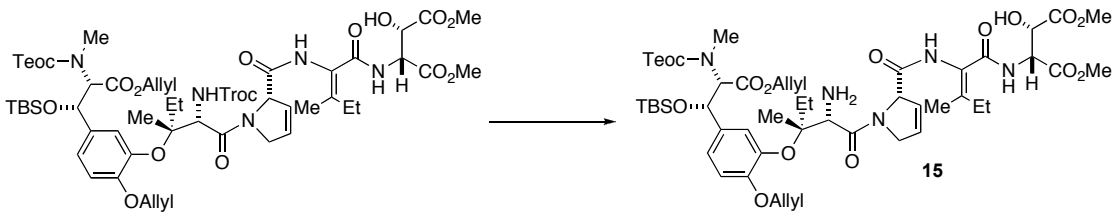
TLC $\mathbf{R}_f$ = 0.39 (10:1 chloroform/methanol)

IR (film): 3363 br m, 2956 m, 2856 m, 1741 s, 1670 m, 1643 m, 1504 s, 1258 s, 1094 m, 840 s, 778 m, 734 m, 558 m.

^{1}H NMR (499.8 MHz, DMSO-d_6, 100 ˚C) δ 8.91 (br, s, 1H), 7.28-7.14 (m, 1H), 7.08-6.96 (m, 3H), 6.14-6.06 (m, 1H), 6.05 (dd, J= 5, 11 Hz, 1 H), 5.98-5.90 (m, 1H), 5.91-5.86 (m, 1H), 5.42-5.31 (m, 2H), 5.28-5.21 (m, 2H) 5.07 (d, J=9 Hz, 1H), 4.86-4.80 (m, 2H), 4.73 (d, J=9 Hz, 1H), 4.70-4.62 (m, 5H), 4.37 (d, J=4 Hz, 1H), 3.96-3.86 (m, 2H), 3.86 (d, J=11 Hz, 1H), 3.79 (d, J=11 Hz, 1H), 3.71-3.67 (m, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 2.73 (s, 3H), 2.63-2.50 (m, 2H), 2.14-2.01 (m, 3H), 1.84-1.78 (m, 1H), 1.71-1.62 (m, 1H), 1.37 (s, 3H), 1.03 (t, J=7 Hz, 3H), 0.89 (t, J=10 Hz, 3H), 0.84-0.80 (m, 2H), 0.80 (s, 9H), 0.02 (s, 3H), -0.01 (s, 9H), -0.21 (s, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6, 100 ˚C): δ 170.3, 168.3, 133.0, 131.7, 127.2, 122.89, 122.5, 117.4, 117.2, 113.2, 95.5, 84.5, 73.8, 71.8, 70.6, 68.9, 64.3, 63.9, 62.6, 54.9, 53.7, 51.2, 51.0, 30.9, 28.1, 25.7, 24.9, 17.0, 16.8, 11.9, 7.7, -2.2, -5.3, -5.8.

HRMS calculated for $C_{54}H_{82}Cl_3N_5O_{17}Si_2$ (M+Na): 1256.4207 amu, found (ESI) 1256.4208 amu.



Compound 15. Nanosize particles of zinc (Aldrich, Saint Louis, MO, 35 nm) were washed by shaking with 0.25 M HCl, filtering, washing with 0.25 M HCl, water, 95% ethanol, and ether, and drying under vacuum. To a flask containing the Troc-protected amine (709.0 mg, 0.574 mmol, 1 equiv), zinc (1.50 g, 22.9 mmol, 40 equiv), and acetic acid (5.74 mL, 0.1 M) were added. After stirring at room temperature in a nitrogen atmosphere for 13 h, 38 equiv more of zinc were added. When the reaction had proceeded for a total of 22 h, the reaction mixture was filtered over a pad of Celite, washed with methanol, and concentrated. The crude material was purified by silica gel chromatography using a mobile phase of 1:2 hexanes/ethyl acetate to 100% ethyl acetate to 20:1 chloroform/methanol. This yielded 465.1 mg (77%) of the desired amine.

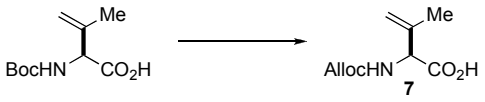
TLC $\mathbf{R}_f$ = 0.36 (10:1 chloroform/methanol)

IR (film): 3357 br w, 2955 m, 2857 m, 1743 s, 1702 s, 1505 s, 1253 s, 1215 m, 1128 m, 839 s, 780 m, 732 w, 695 w.

^{1}H NMR (499.8 MHz, $CDCl_3$) δ 7.04-6.76 (m, 3H), 6.10-5.86 (m, 2H), 5.41-5.28 (m, 2H), 5.27-5.20 (m, 1H), 5.12-4.95 (m, 2H), 4.72-4.43 (m, 6H), 4.18-4.08 (m, 1H), 4.07-3.97 (m, 1H), 3.96-3.83 (m, 2H), 3.82-3.64 (m, 6H), 2.82-2.70 (m, 3H), 2.00 (2, 6H), 1.76-1.70 (m, 2H), 1.30-0.98 (m, 6H), 0.93-0.75 (m, 11H), 0.04-(-0.07) (m, 12H), (-0.23)-(-0.28) (m, 3H).

^{13}C NMR (125.7 MHz, $CDCl_3$, 25 ˚C): δ 176.3, 171.4, 169.6, 168.4, 165.3, 156.2, 155.7, 152.5, 152.2, 133.6, 132.5, 131.9, 131.7, 127.6, 125.1, 123.5, 119.3, 118.8, 118.5, 112.5, 85.8, 72.8, 71.2, 69.7, 69.6, 65.6, 64.0, 63.9, 57.4, 56.2, 54.6, 53.1, 53.0, 52.6, 52.4, 31.8, 27.1, 25.5, 21.4, 18.6, 17.9, 17.5, 15.0, 12.8, 11.5, 8.6, -1.5, -4.6, -5.3.

HRMS calculated for $C_{51}H_{81}N_5O_{15}Si_2$ (M+H):1060.5338 amu, found (ESI) 1060.5346 amu.



7

(*S*)-2-Allyloxycarbonylamino-3-methyl-but-3-enoic acid (7). Boc-ΔVal-OH (201.7 mg, 0.937 mmol, 1 equiv) was dissolved in dichloromethane (10 mL) in a nitrogen atmosphere. The solution was cooled to 0 ˚C and then trifluoroacetic acid (2 mL, 17% solution, 0.08 M) was added. After stirring at 0 ˚C for 5 h, the reaction mixture was concentrated to leave the crude ΔVal-OH. To a flask containing the crude intermediate, 1,4-dioxane (6 mL), water (4.6 mL), and sodium carbonate (496.6 mg, 4.69 mmol, 5 equiv) were added. This solution was stirred at room temperature under a nitrogen atmosphere. A solution of Alloc-OSu (279.9 mg, 1.41 mmol, 1.5 equiv) dissolved in 1,4-dioxane was added to the reaction mixture. Then 1,4-dioxane was added to bring the reaction to its final volume (13.8 mL of 2:1 1,4-dioxane/water, 0.07 M). After stirring for 30 min at room temperature, dichloromethane (10 mL) and water (10 mL) were added and the phases were separated. The aqueous layer was acidified to pH 1 with 1 M HCl and extracted with dichloromethane (6 × 10 mL). These organic extracts were combined and dried with anhydrous sodium sulfate to give 141.6 mg (76%) of Alloc-ΔVal-OH **7**. The preparation of the starting material Boc-ΔVal-OH is described elsewhere.[6]

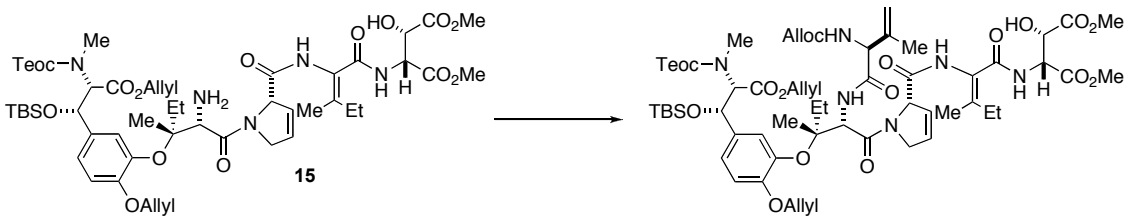
TLC R_f = 0.19 (5:1 chloroform/methanol)

IR (film): 3333 br m, 2953 br m, 1714 s, 1518 m, 1235 m, 1059 m, 993 m, 915 m, 737 m.

^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ˚C): δ 11.10 (s, 1H), 5.94-5.66 (m, 1H), 5.33-5.23 (m, 1H), 5.22-5.17 (m, 1H), 5.12 (s, 1H), 5.04 (s, 1H), 4.85-4.66 (m, 1H), 4.61-4.52 (m, 2H), 1.81 (s, 3H).

^{13}C NMR (100.6, $CDCl_3$, 25 ˚C): δ 174.5, 173.4, 156.9, 155.5, 140.1, 139.6, 132.3, 131.8, 118.0, 115.5, 66.5, 66.0, 59.8, 59.1, 28.7, 28.3, 19.3, 19.1.

HRMS calculated for $C_9H_{13}NO_4$ (M+Na): 222.0740 amu, found (ESI) 222.0742 amu.



ΔVal coupling. To a 10-mL flask containing free amine **15** (6.9 mg, 0.00651 mmol, 1 equiv) was added Alloc-ΔVal-OH **7** (1.9 mg, 0.00976 mmol, 1.5 equiv) before dissolving the solute in acetonitrile (100 μL). Next, PyBOP (6.8 mg, 0.0130 mmol, 2 equiv) was added followed by *N,N*-diisopropylethylamine (4.5 μL, 0.0260 mmol, 4 equiv). This mixture was stirred at room temperature for 1 h before diluting the reaction with dichloromethane (3 mL). The reaction was quenched with 1 M HCl (2 mL) and then the two layers were separated. The aqueous layer was extracted with dichloromethane (3 × 2 mL). The organics were combined, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to leave a crude film. This material was purified by silica gel column chromatography using a stepwise mobile phase gradient of 2:1 to 1:4 hexanes/ethyl acetate to yield the hexapeptide (6.4 mg, 0.00515 mmol, 79%).

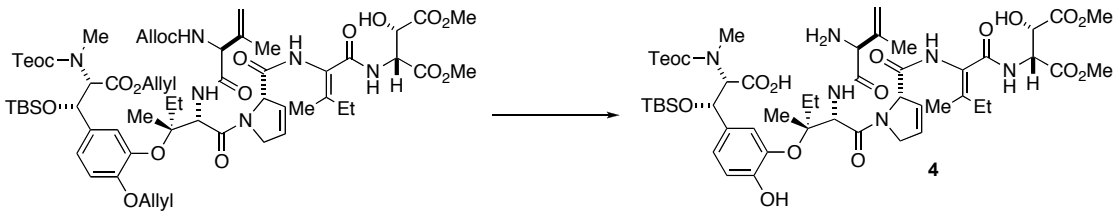
TLC $\mathbf{R}_f$ = 0.17 (1:2 hexanes/ethyl acetate)

IR (film): 3383 w, 1918 m, 2850 m, 1741 m, 1675 m, 1497 m, 1265 s, 844 s, 738 s, 703 m.

^{1}H NMR (499.8 MHz, CD_3OD) δ 7.16-6.94 (m, 3H), 6.18-6.04 (m, 1H), 6.00-5.86 (m, 1H), 5.44-5.21 (m, 2H), 5.20-5.01 (m, 2H), 4.95-4.76 (m, 2H), 4.66-4.46 (m, 6H), 4.05-3.93 (m, 1H), 3.68-3.64 (m, 2H), 3.58-3.50 (m, 2H), 2.82-2.76 (m, 2H), 2.55-2.48 (m, 1H), 2.22-2.07 (m, 1H), 1.82 (s, 3H), 1.77 (s, 3H), 1.54-1.44 (m, 2H), 1.11 (t, J=7.5 Hz, 3H), 0.90-0.78 (m, 11H), 0.07-(-0.05) (m, 12H), (-0.19)-(-0.24) (m, 3H).

^{13}C NMR (125.7 MHz, CD_3OD, 25 ˚C): δ 172.3, 171.0, 160.7, 166.8, 158.0, 154.1, 143.4, 142.0, 134.9, 134.3, 133.3, 129.9, 125.6, 118.8, 117.7, 115.6, 114.3, 86.6, 74.0, 73.6, 72.1, 70.9, 70.8, 69.7, 66.8, 66.6, 65.7, 65.4, 65.2, 61.5, 57.6, 55.9, 52.9, 52.7, 30.0, 28.0, 26.2, 21.4, 20.9, 19.9, 18.8, 18.5, 14.5, 13.1, 9.6, -1.4, -4.1, -5.0.

HRMS calculated for $C_{60}H_{92}N_6O_{18}Si_2$ (M+Na): 1263.5918 amu, found (ESI) 1263.5904 amu.



Compound 4. To the fully protected hexapeptide (197.6 mg, 0.159 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 18.4 mg, 0.0159 mmol, 0.1 equiv) and this mixture was dissolved in dichloromethane (1.6 mL, 0.1 M). Then acetic acid (72.9 µL, 1.27 mmol, 8 equiv) and tri-*n*-butyltin hydride (257 µL, 0.955 mmol, 6 equiv) were added dropwise. The evolution of gas was observed. After stirring the reaction at room temperature in a nitrogen atmosphere for 1 h, the reaction was diluted with dichloromethane (10 mL) and 1 M HCl was added (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. Purification by silica gel chromatography using a stepwise mobile phase gradient of 100:1 to 10:1 chloroform/methanol produced 126.1 mg (74%) of the amino acid. $Pd(PPh_3)_4$ was freshly made from palladium(II) chloride and triphenylphosphine; tri-*n*-butyltin hydride was purified by distillation at reduced pressure.[7]

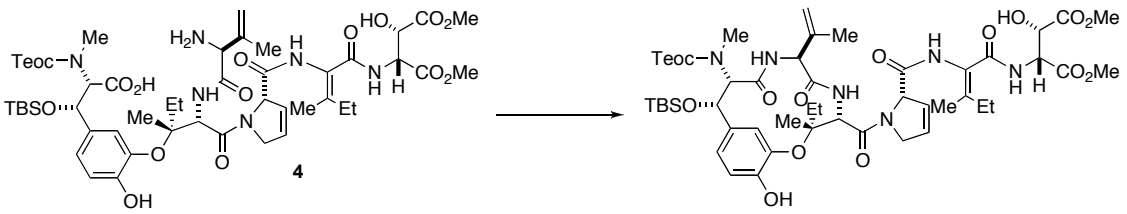
TLC R_f = 0.31 (10:1 chloroform/methanol)

IR (film): 3280 br m, 2954 m, 2854 m, 1749 m, 1644 s, 1507 s, 1440 m, 1285 m, 1251 m, 1215 m, 1117 m, 840 s, 778 m, 735 m.

^{1}H NMR (499.8 MHz, CD_3OD): δ 7.92-7.70 (m, 2H), 7.07-6.93 (m, 2H), 6.72 (dd, J=2, 8 Hz, 1H), 6.09 (s, 1H), 5.94 (S, 1H), 5.29-5.18 (m, 2H), 5.16-5.04 (m, 2H), 5.02-4.80 (m, 4H), 4.60-4.50 (m, 2H), 4.41-4.30 (m, 1H), 4.05-3.80 (m, 2H), 3.79-3.58 (m, 6H), 2.72-2.64 (m, 2H), 2.58-2.42 (m, 1H), 2.10-1.88 (m, 2H), 1.86-1.76 (m, 5H), 1.68-1.76 (m, 5H), 1.68-1.59 (m, 1H), 1.38-1.03 (m, 6H), 1.01-0.76 (m, 14H), 0.08-(-0.06) (m, 12H), (-0.14)-(-0.21) (m, 3H).

^{13}C NMR (125.7 MHz, CD_3OD, 25 ˚C): δ 172.8, 171.1, 170.7, 170.4, 167.4, 158.5, 158.4, 152.3, 152.0, 148.1, 147.8, 142.1, 141.9, 141.7, 135.1, 134.0, 131.5, 131.4, 129.5, 126.1, 125.6, 125.2, 124.2, 117.4, 116.8, 116.3, 85.9, 85.7, 75.0, 74.7, 72.3, 69.1, 65.0, 64.8, 60.3, 58.3, 57.3, 55.9, 53.0, 52.8, 32.1, 29.2, 28.2, 28.0, 26.4, 19.9, 19.0, 18.5, 18.4, 14.1, 13.1, 9.8, -1.4, -4.4, -4.7.

HRMS calculated for $C_{50}H_{80}N_6O_{16}Si_2$ (M+Na): 1099.5081 amu, found (ESI) 1099.5067 amu.



Macrocyclization. To a flask containing amino acid **4** (49.5 mg, 0.046 mmol, 1 equiv), DMF (15.3 mL, 0.003 M), PyAOP (47.9 mg, 0.092 mmol, 2 equiv), and *N*,*N*-diisopropylethylamine (30.4 μL, 0.184 mmol, 4 equiv) were added. After stirring for 70 min at room temperature in a nitrogen atmosphere, the reaction was concentrated to remove the solvent. The crude material was diluted with dichloromethane (10 mL) and then 1 M HCl was added (10 mL); the phases were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried with sodium sulfate, concentrated, and purified by silica gel chromatography using a stepwise mobile phase gradient of 1:2 hexanes/ethyl acetate to 100% ethyl acetate to 50:1 chloroform/methanol. This yielded 23.5 mg (48%) of the macrocyclized product.

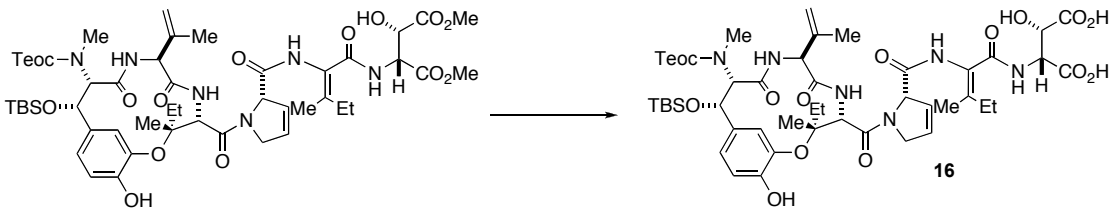
TLC $\mathbf{R}_f$ = 0.42 (10:1 chloroform/methanol)

IR (film): 3406 br w, 3055 m, 2926 m, 2853 m, 1673 m, 1496 m, 1440 m, 1265 s, 1213 m, 1095 m, 847 m, 739 s, 704 m.

^{1}H NMR (499.8 MHz, CD_3OD, 25 ˚C): δ 7.76-7.60 (m, 3H), 7.07-6.84 (m, 2H), 6.78-6.67 (m, 1H), 6.16-6.03 (m, 1H), 5.98-5.89 (m, 1H), 5.30-4.88 (m, 4H), 4.64-4.47 (m, 2H), 4.23-3.89 (m, 1H), 3.80-3.63 (m, 6H), 3.17-3.05 (m, 1H), 2.81-2.71 (m, 1H), 2.61-2.42 (m, 1H), 2.13-1.99 (m, 2H), 1.88-1.74 (m, 3H), 1.73-1.61 (m, 3H), 1.41-1.19 (m, 6H), 1.14-0.96 (m, 6H), 0.94-0.83 (m, 9H), 0.81-0.69 (m, 6H), 0.11-(-0.06) (m, 12H), (-0.08)-(-0.27) (m, 3H).

^{13}C NMR (125.7 MHz, CD_3OD, 25 ˚C): δ 173.8, 170.4, 167.3, 164.9, 161.3, 154.5, 144.1, 141.1, 136.3, 135.1, 133.8, 133.0, 131.5, 129.9, 123.6, 120.2, 119.5, 116.8, 85.3, 72.4, 68.7, 65.3, 57.1, 55.9, 53.0, 52.9, 47.3, 36.9, 31.6, 29.1, 27.9, 27.0, 26.6, 26.4, 26.2, 20.1, 19.5, 18.9, 14.0, 13.1, 12.1, 8.2, -1.4, -4.7, -5.1.

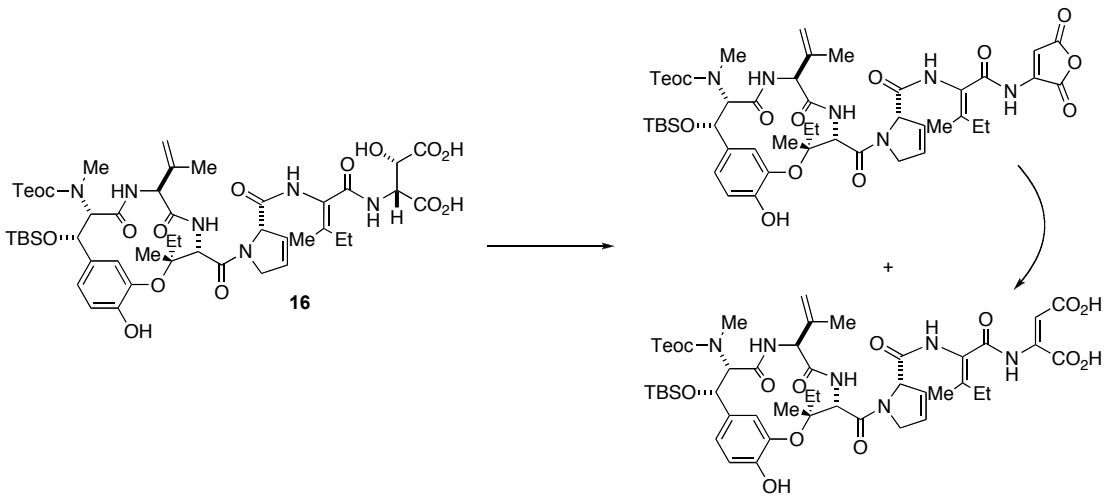
HRMS calculated for $C_{50}H_{78}N_6O_{15}Si_2$ (M+Na): 1081.4967 amu, found (ESI) 1081.4961 amu.



Methyl ester hydrolysis. The macrocycle (53.0 mg, 0.050 mmol, 1 equiv) was dissolved in THF (5.0 mL, 0.01 M). A freshly prepared aqueous solution of lithium hydroxide (0.5 M, 400 μL, 0.200 mmol, 4 equiv) was added dropwise. The reaction was immediately warmed to room temperature and stirred in a nitrogen atmosphere for 75 min. Then dichloromethane (10 mL) and 1 M HCl (5 mL) were added; the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried with anhydrous sodium sulfate, and concentrated to give 36.1 mg of the crude bis-acid **16**. The product was too polar to visualize by TLC or purify by normal phase chromatography. It was used in the next step without further purification.

IR (film): 3396 br m, 2918 s, 2850 m, 1644 m, 1508 m, 1412 m, 1247 m, 1211 m, 1121 m, 843 s, 730 m, 695 m, 558 m.

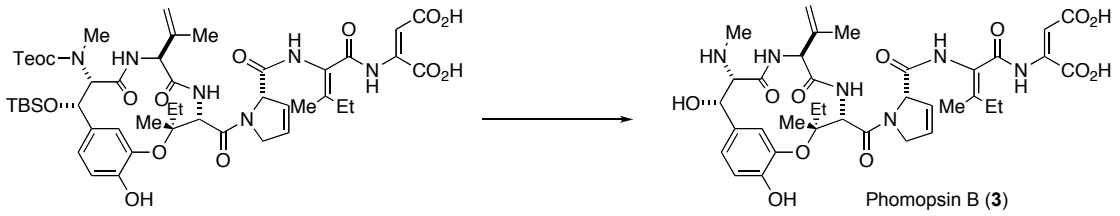
HRMS calculated for $C_{48}H_{74}N_6O_{15}Si_2$ (M-H): 1029.4669 amu, found (ESI) 1029.4672 amu.



Asp dehydration. Since this reaction could not be followed by TLC, we minotired the reaction progress of a model compound by HPLC to estimate reaction times. We noticed that prolonged exposure to lithium hydroxide in the second step forms the thermodynamic *Z*-ΔAsp adduct. To the bis-acid **16** (34.0 mg, 0.033 mmol, 1 equiv) was added pyridine (330 μL, 0.1 M) and the solution was cooled to 0 ˚C. Following the addition of acetic anhydride (distilled over calcium hydride, 12.4 μL, 0.132 mmol, 4 equiv), the reaction was stirred at 0 ˚C for 90 min under nitrogen until it was concentrated. The crude material was dissolved in THF (4.7 mL, 0.007 M) and a freshly prepared aqueous solution of lithium hydroxide (0.5 M, 0.132 mmol, 264 μL) was added. After stirring at room temperature for 15 min in an atmosphere of nitrogen, 1 M HCl (10 mL) and dichloromethane (10 mL) were added. The layers were separated, the aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried with sodium sulfate, and concentrated to yield 26.0 mg of the crude dehydrated material. The product was too polar to visualize by TLC or purify by normal phase chromatography. It was used in the next step without further purification.

IR (film): 3281 br m, 2955 m, 2927 m, 2854 m, 1680 s, 1644 s, 1507 s, 1439 m, 1377 m, 1252 m, 1212 m, 1155 m, 1090 m, 842 s, 779 m, 734 m, 696 m, 558 m.

HRMS calculated for $C_{48}H_{72}N_6O_{14}Si_2$ (M-H): 1011.4565 amu, found (ESI) 1011.4567 amu.



Phomopsin B (3). The protected amino alcohol (26.0 mg, 0.0257 mmol, 1 equiv) was dissolved in DMF (300 μL). The hygroscopic TAS-F (70.7 mg, 0.257 mmol, 10 equiv) was dissolved in DMF and added to the reaction dropwise; DMF was added to bring the reaction to its final volume (611 μL, 0.042 M). After stirring at room temperature in a nitrogen atmosphere for 14 h, 1 M HCl (800 μL) was added and the solution was concentrated. The crude material was purified using three C18 Sep-Pak columns. Each column was activated by treatment with methanol (5 mL) followed by water (10 mL). The crude material was dissolved in water (1.5 mL) and one third was loaded onto each of the three columns. Water (10 mL) was passed through each column to elute any salts, followed by 1:1 water/methanol (20 mL) to elute phomopsin B, and finishing with methanol (10 mL) to elute impurities. The water/methanol fractions were combined and concentrated to yield 7.5 mg of impure phomopsin B (17% over 3 steps). The product was too polar to visualize by TLC or purify by normal phase chromatography. The crude material was purified by reverse phase HPLC using a Higgins Analytical (Mountain View, CA) Targa C18 5 μm column. The flow was at 1 mL/min of an isocratic mobile phase of 80% water (+ 0.1% formic acid) and 20% acetonitrile (+ 0.1% formic acid) with detection at 285 nm.

NMR spectra (1D ^{1}H, 2D ^{1}H-^{13}C HSQC, 2D ^{1}H-^{13}C HMBC) were acquired at the Stanford Magnetic Resonance Laboratory on a Varian Inova 800 MHz instrument at 25 ˚C using a 5 mm H{CN} Z-axis gradient Cold Probe (Varian, Inc., Palo Alto, CA). Several deuterated solvents were investigated. Since the HPLC conditions showed the two samples to be identical, CD_3CN was investigated, but the spectra were not superimposable. Even when doped with D_2O, the spectra were not identical. The natural and synthetic samples were then mixed in approximately equimolar amounts to generate a mixed sample. In our final conditions, the samples were dissolved in 300 μL of 10:1 CD_3CN/D_2O and placed in a symmetrical microtube (Shigemi, Allison Park, PA). An external reference of TSP in 10:1 CD_3CN/D_2O was used to set the acetonitrile solvent signal to 1.988 ppm in the ^{1}H dimension and 3.22 and 120.52 ppm in the ^{13}C dimension. The impurities in the spectra for the synthetic sample at 8.44 and 3.11-3.63 ppm

^{1}H were not present in the crude eluent from the Sep-Pak columns, but appeared after purification and extensive physical manipulations.

IR (prior to HPLC purification, film): 3424 br s, 2917 s, 2849 m, 1640 m, 1462 w, 1440 w, 1210 m, 1121 m, 1089 m, 1015 m, 842 w, 805 w, 731 m, 695 m.

HRMS calculated for $C_{36}H_{46}N_6O_{12}$ (M-H): 753.3095 amu, found (ESI) 753.3095 amu.

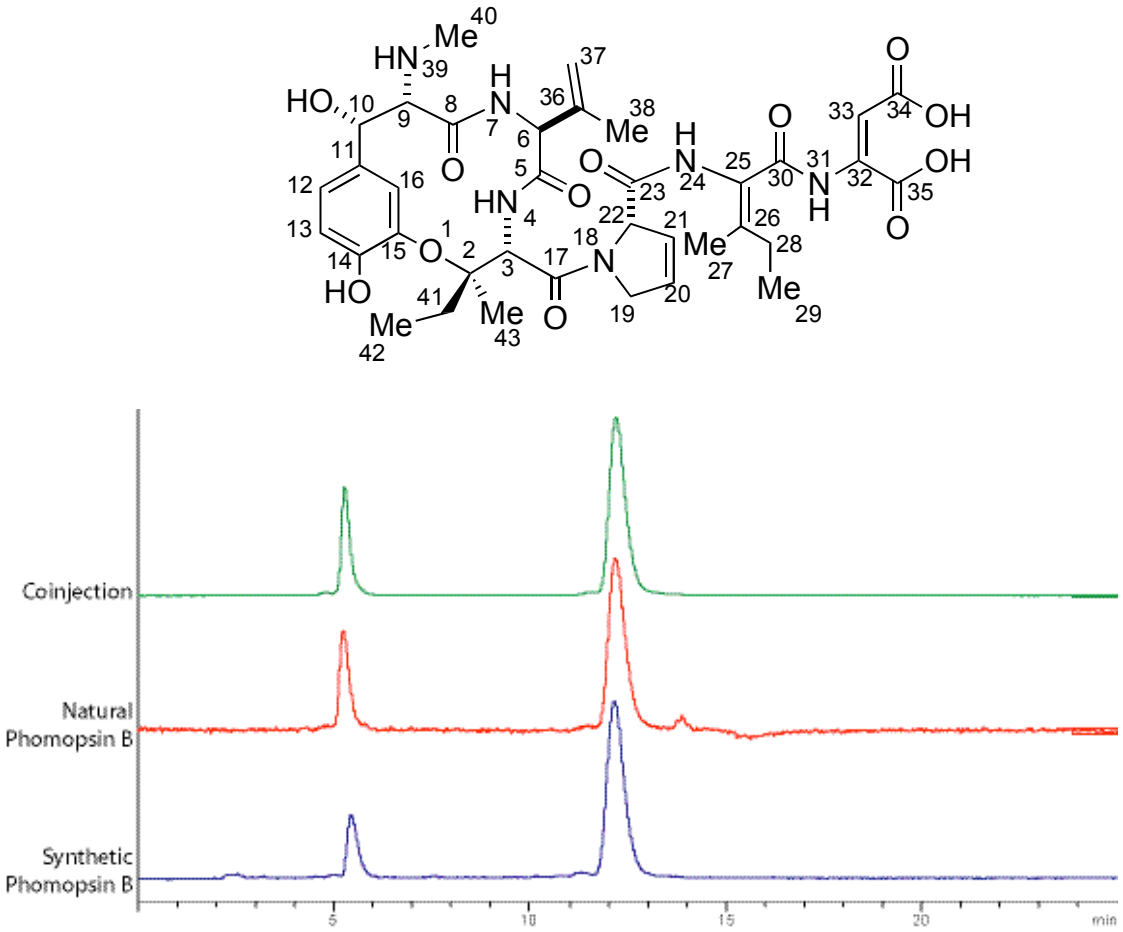


Figure S1. Comparison of the natural, synthetic, and mixed phomopsin B samples by HPLC under the following conditions: Higgins Analytical Targa C18 5 μm column, 1 mL/min flow rate, isocratic mobile phase of 80% water (+ 0.1% formic acid) and 20% acetonitrile (+ 0.1% formic acid), and 285 nm detection.

An aliquot of phomopsin B was purified by HPLC using the aforementioned conditions to separate peak A (retention time of 5.45 min) and peak B (retention time of 12.13 min). These two samples were concentrated to dryness, dissolved in a solution of 4:1 water/acetonitrile (t=0), and reinjected onto the HPLC to monitor the relative amounts of peaks A and B over the next four days.

Table S1. Results of phomopsin B peak interconversion as measured by HPLC.

Isolated Peak	Time (h)	Area % peak A	Area % peak B
peak A	0	94.8	5.2
peak A	30	93.1	6.9
peak A	46.5	92.4	7.6
peak A	70.5	91.4	8.6
peak A	94.5	90.0	10.0
peak B	0	11.7	88.3
peak B	30	16.6	83.4
peak B	46.5	17.0	83.0
peak B	70.5	16.5	83.5
peak B	94.5	16.7	83.3

Table S2. NMR chemical shifts for the natural, synthetic, and mixed phomopsin B samples.

	^{1}H (ppm)			^{13}C (ppm)		
Carbon No.	Natural	Synthetic	Mix	Natural	Synthetic	Mix
2				87.43	87.69	87.58
3	5.00	4.91	4.93	59.12	58.72	58.97
5				171.84	171.97	172.12
6	4.91	4.81	4.83	60.74	61.36	61.33
8				ND	ND	ND
9	4.20	4.21[a]	4.21	70.86	70.55[a]	71.02
10	4.92	4.94	4.93	75.67	75.76	75.79
11				135.33	135.73	135.73
12	7.31	7.59	7.51	124.73	124.83	124.83
13	6.88	6.90	6.89	125.40	125.59	125.61
14				152.44	152.65	152.65
15				145.60	145.64	145.72
16	6.86	6.87	6.86	119.40	119.38	119.42
17				171.10	171.58	171.13
19a[b]	4.70	4.72	4.71	57.65	57.49	57.61
19b[b]	4.63	4.60	4.60			
20	6.00	6.00	6.00	127.99	127.82	127.93
21	6.09	6.09	6.09	131.18	131.08	131.13
22	5.25	5.34	5.31	70.22	70.27	70.25
23				ND	ND	ND
25				150.57	151.34	150.99
26				126.40	126.15	126.26
27	1.83	1.82	1.82	21.07	21.18	21.24
28a[b]	2.48	2.49[c]	2.51	29.57	29.50	29.56
28b[b]	2.45	2.49[c]	2.47			
29	1.11	1.11	1.11	15.01	14.90	14.97
30				ND	ND	ND
32				142.72	ND	ND
33	7.36	7.35	7.31	113.59	113.53	113.71
34,35[d]				168.15	ND	ND
36				142.75	142.56	142.71
37a[b]	4.95	4.96	4.96	116.17	116.82	116.80
37b[b]	4.92	4.91	4.91			
38[e]	1.60	1.63	1.66	22.60	23.16	23.85
38[e]	1.62	1.62	1.62	21.85	21.82	22.45
40	2.32	2.30	2.29	36.04	35.92	35.97
41a[b]	2.09	2.06	2.06	32.73	32.17	32.43
41b[b]	1.70	1.72	1.72			
42	0.98	0.94	0.95	10.55	10.59	10.66
43	1.29	1.29	1.29	32.05	31.98	32.00

ND, not detected. [a] This is a weak signal. [b] These are diastereomeric protons. [c] These are degenerate signals. [d] The assignment of these carbon atoms could not be separated. [e] Two signals are observed due to hindered rotation of the ΔVal residue.

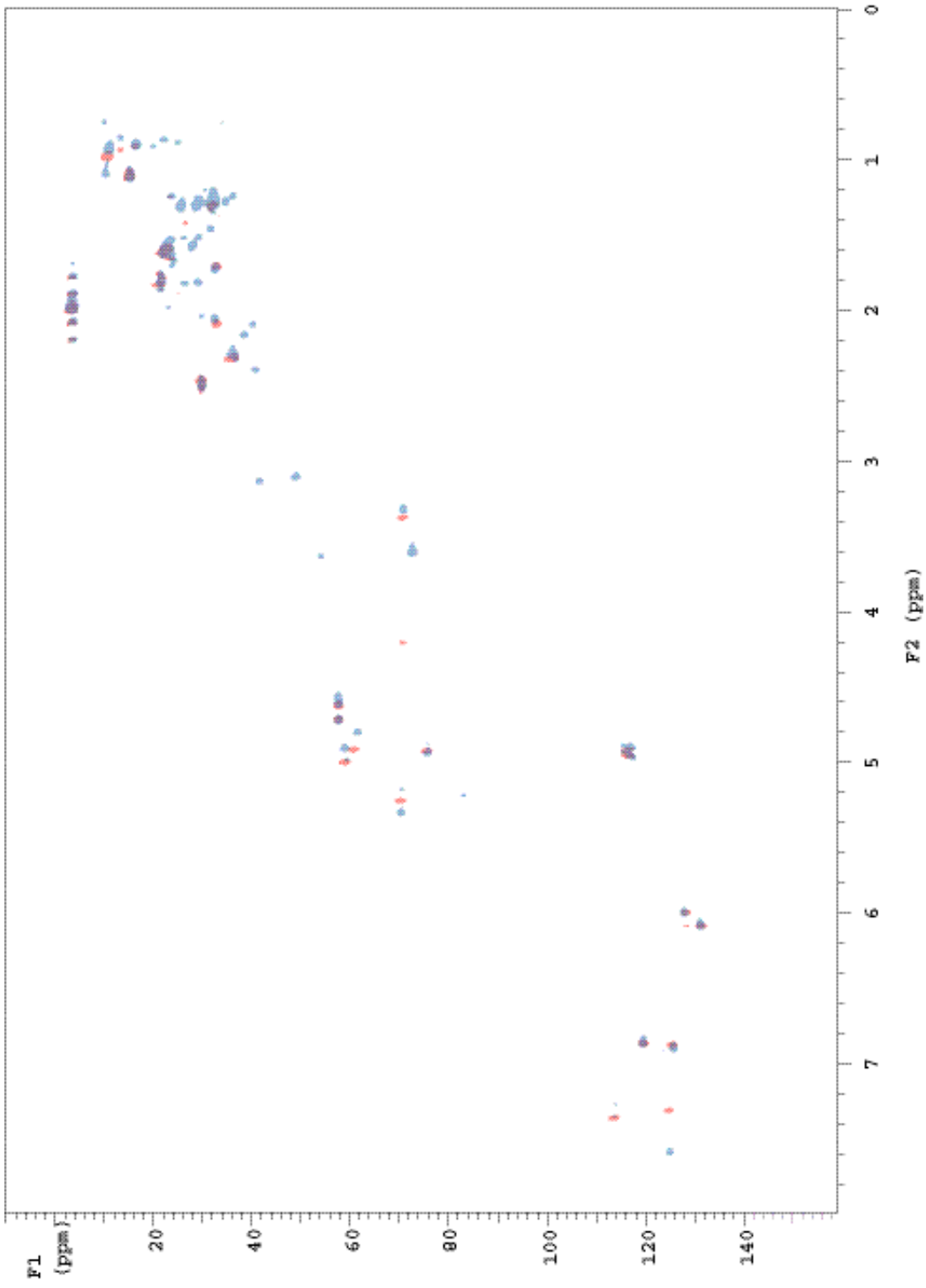


Figure S2. An overlay of the 2D ^{1}H-^{13}C HSQC spectra of the natural (red) and synthetic (blue) phomopsin B samples.

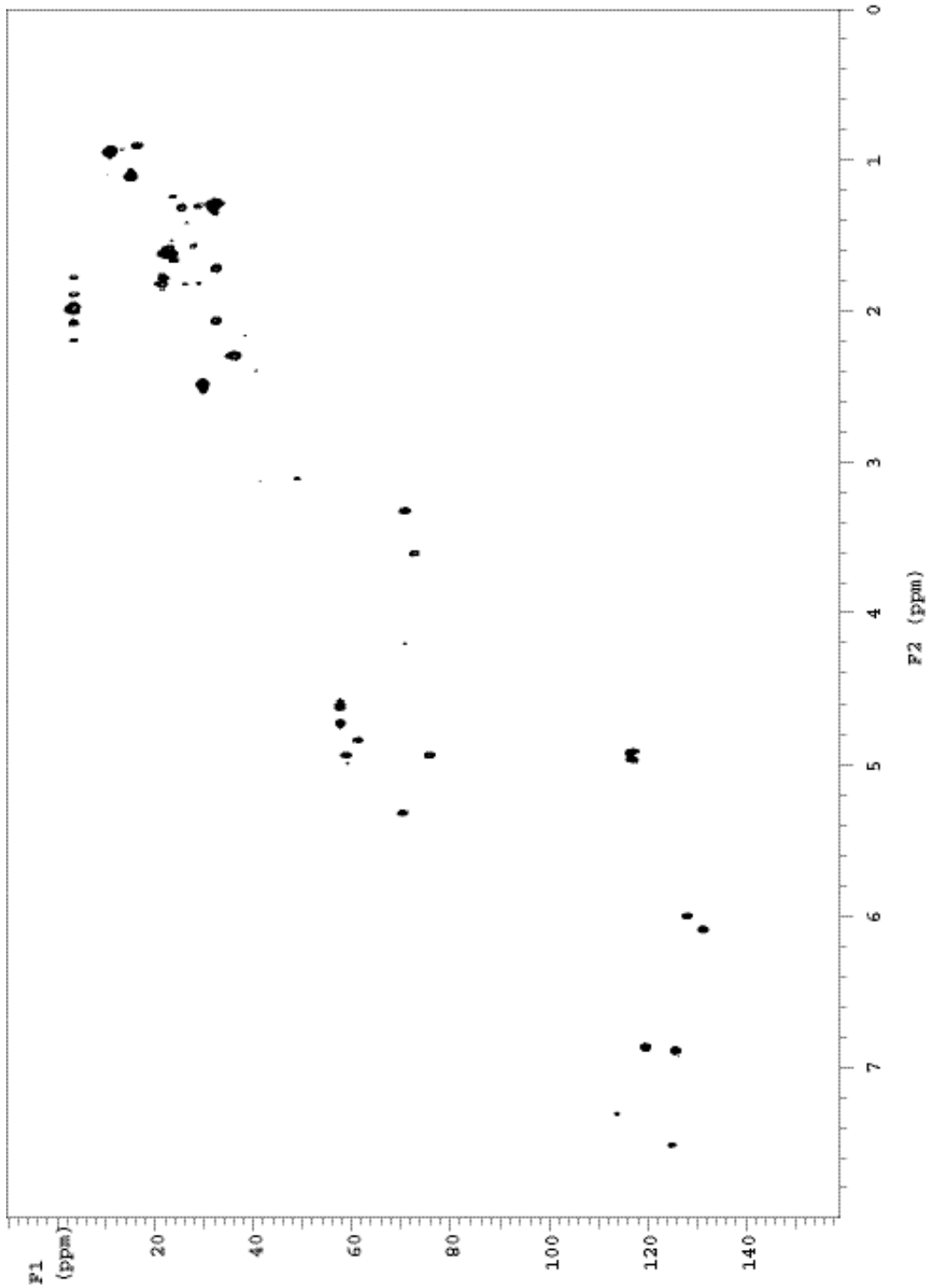


Figure S3. The 2D ^{1}H-^{13}C HSQC spectrum of the mixed natural and synthetic phomopsin B sample.

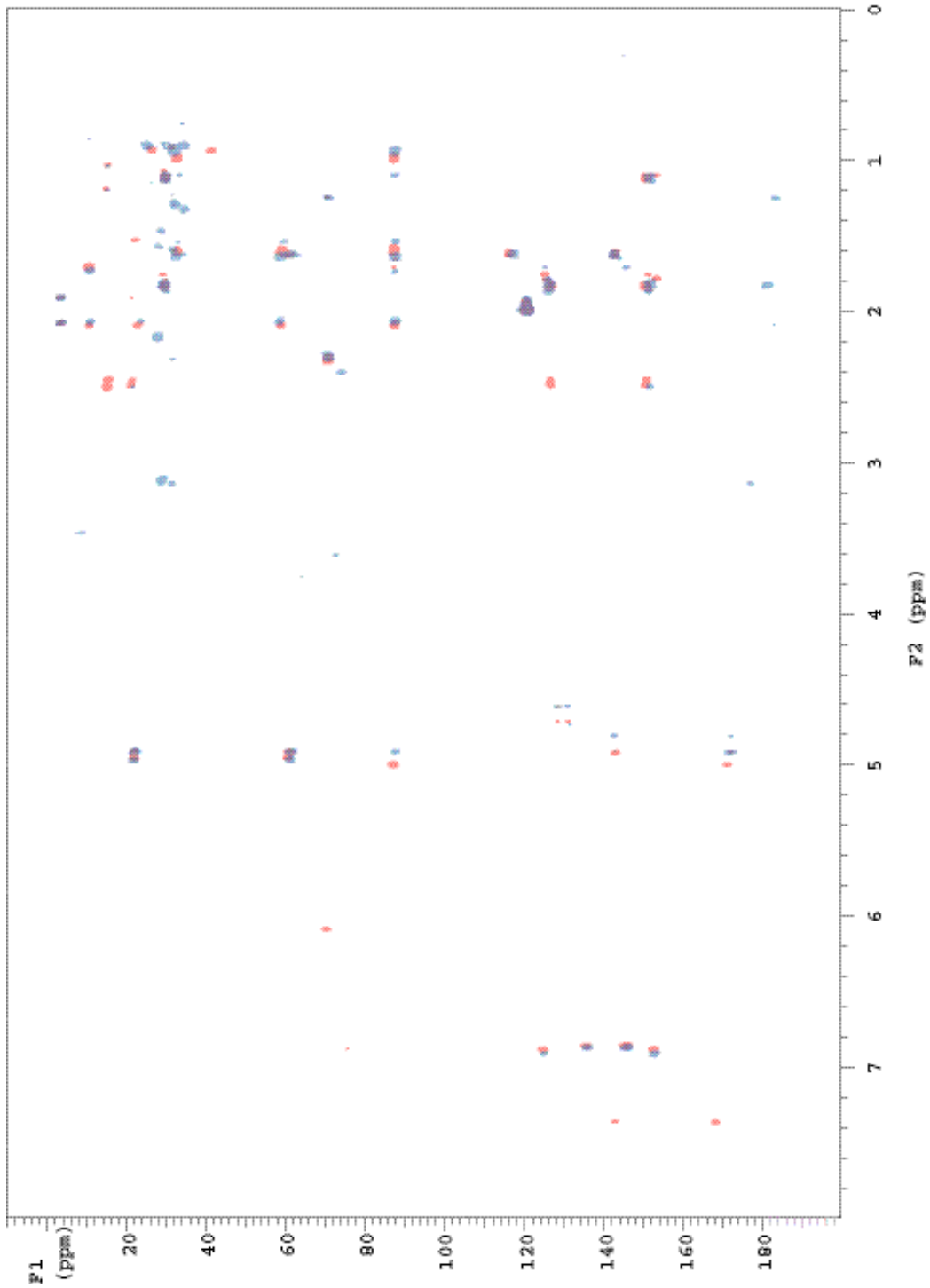


Figure S4. An overlay of the 2D ^{1}H-^{13}C HMBC spectra of the natural (red) and synthetic (blue) phomopsin B samples.

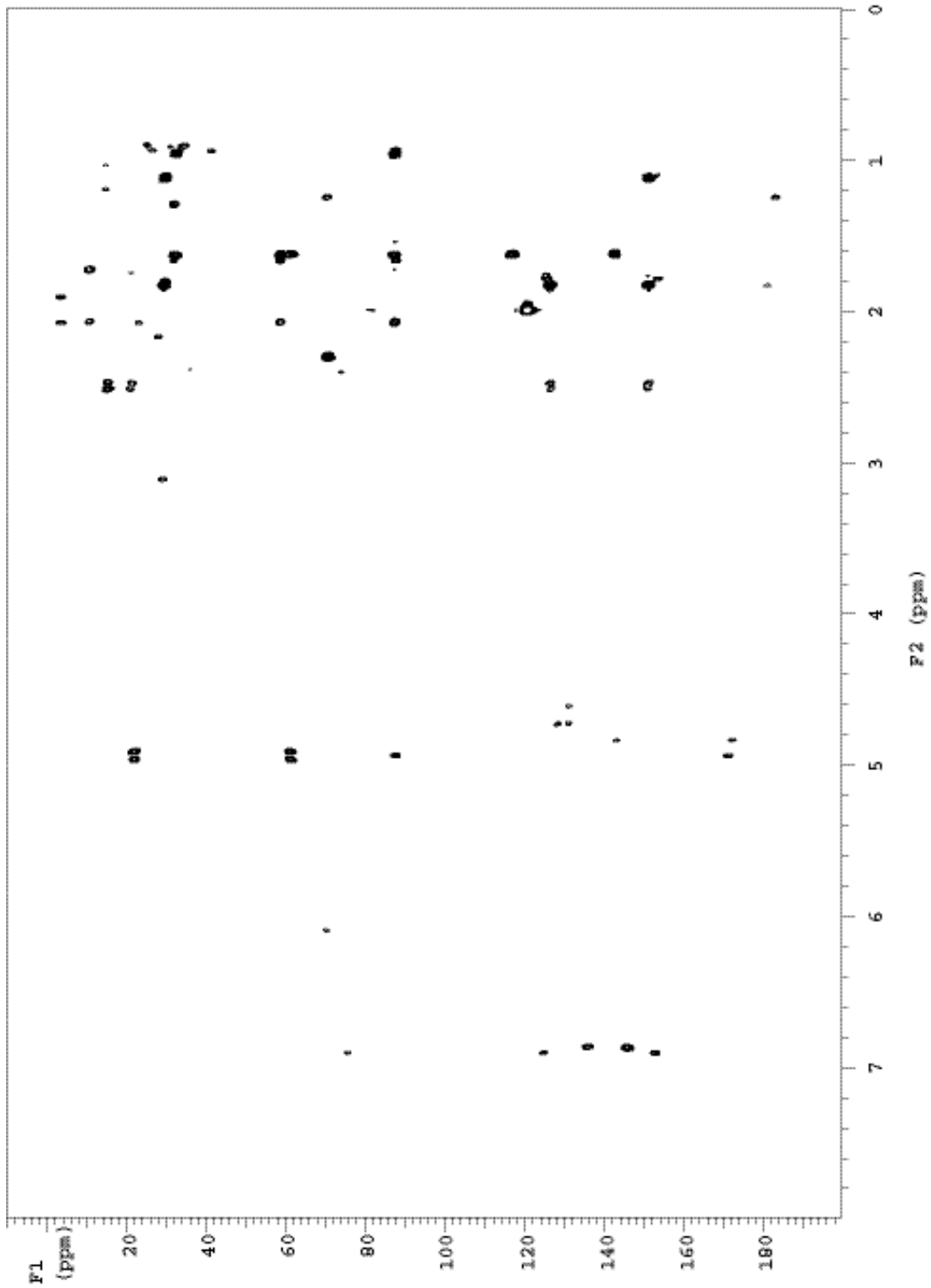
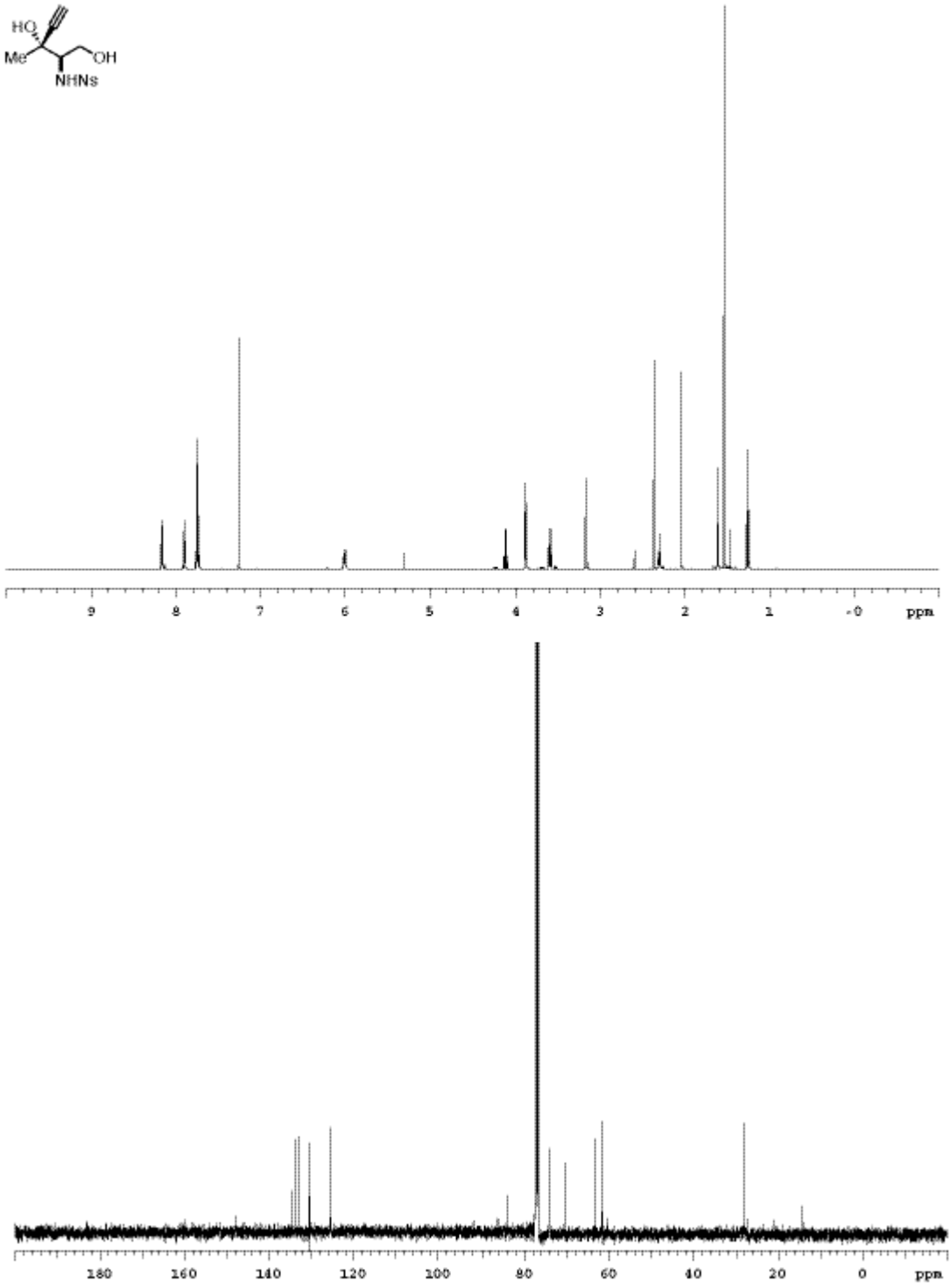
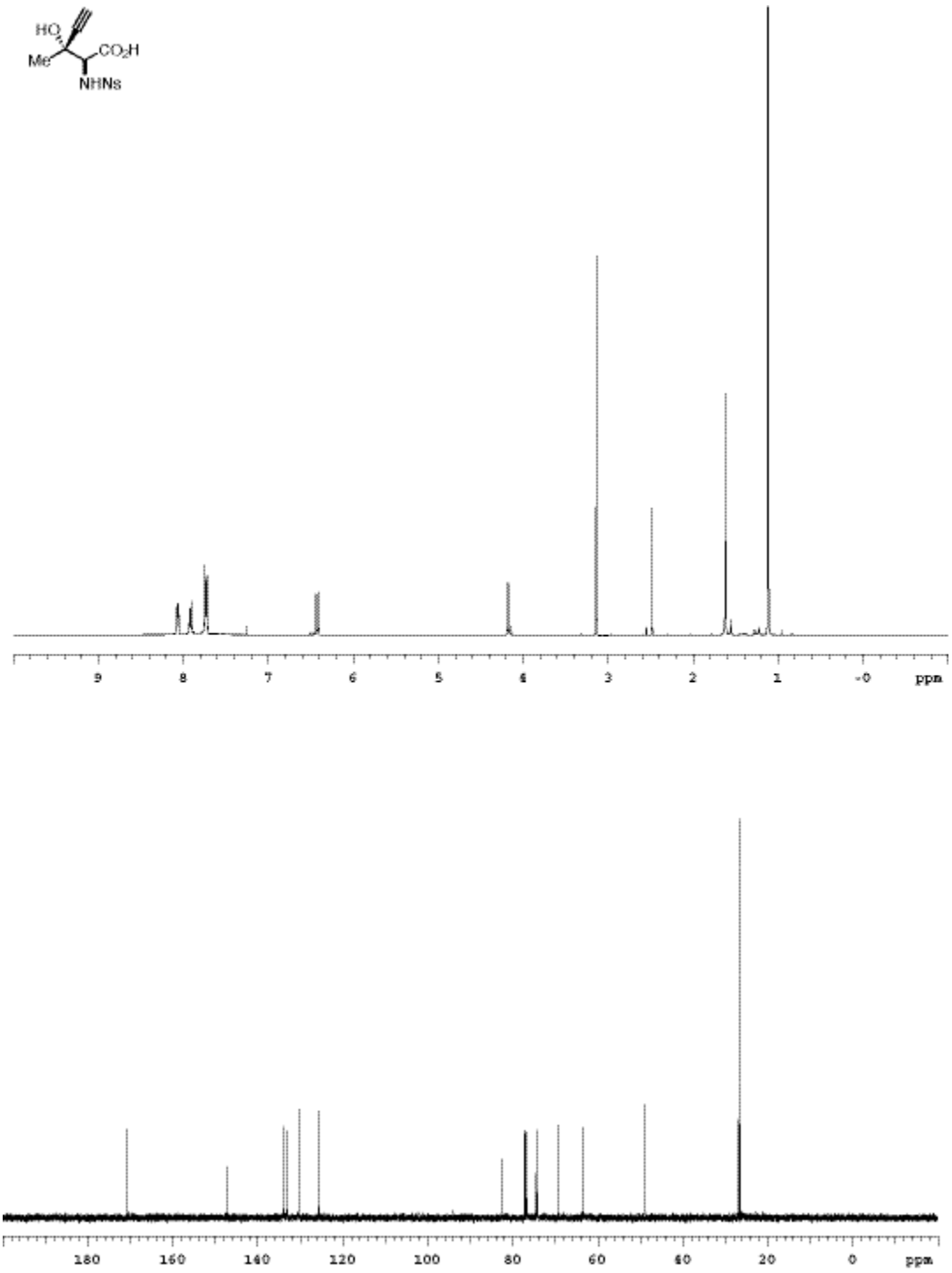


Figure S5. The 2D ^{1}H-^{13}C HMBC spectrum of the mixed natural and synthetic phomopsin B sample.

Selected Spectra

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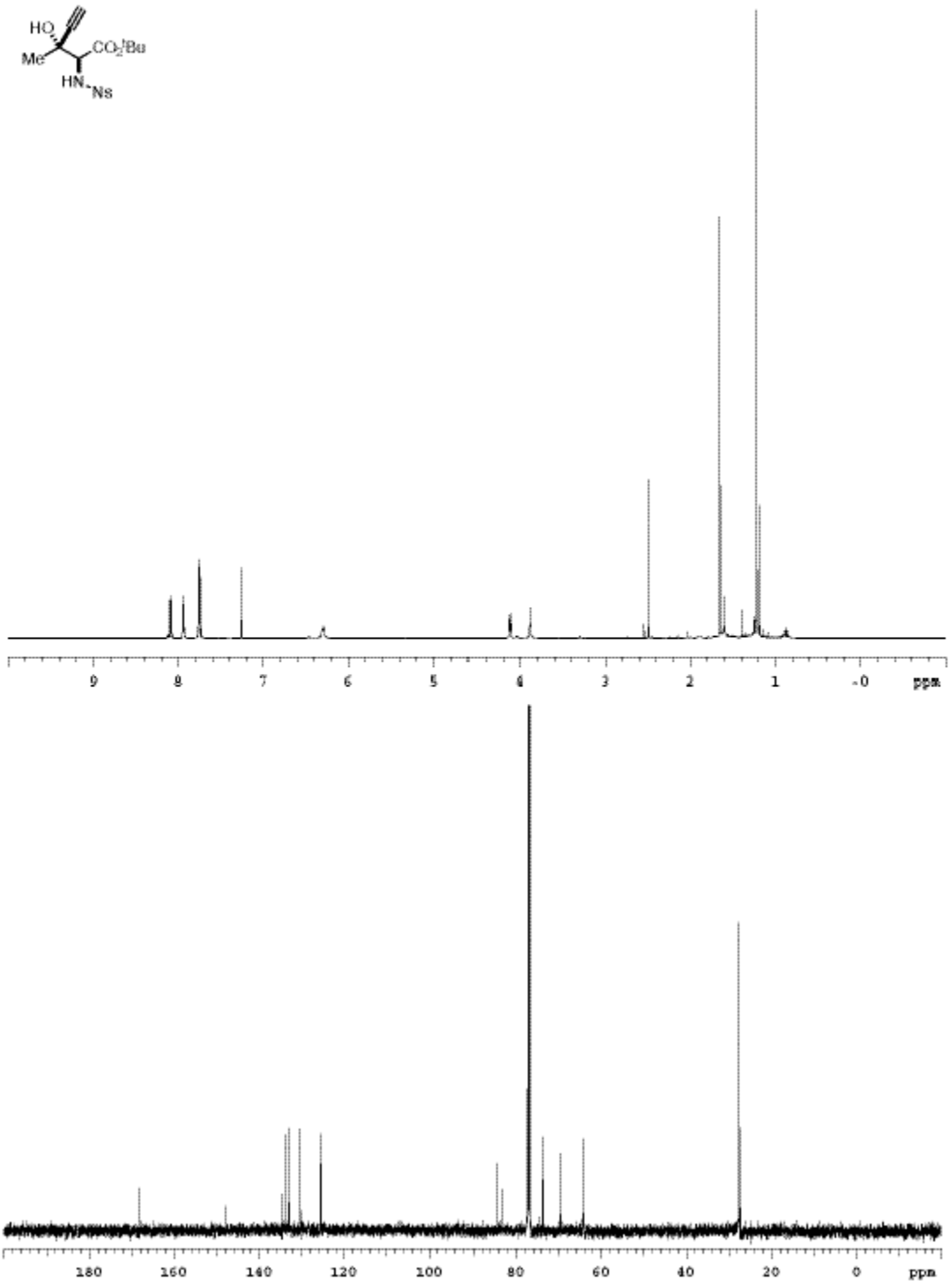
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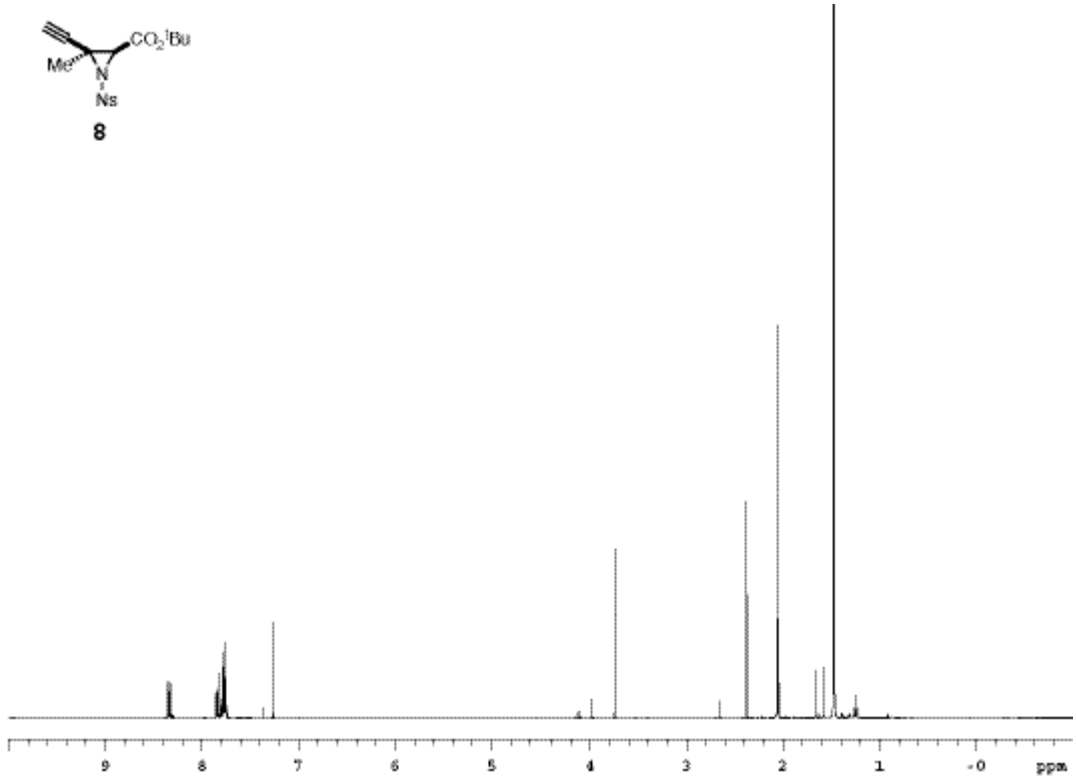
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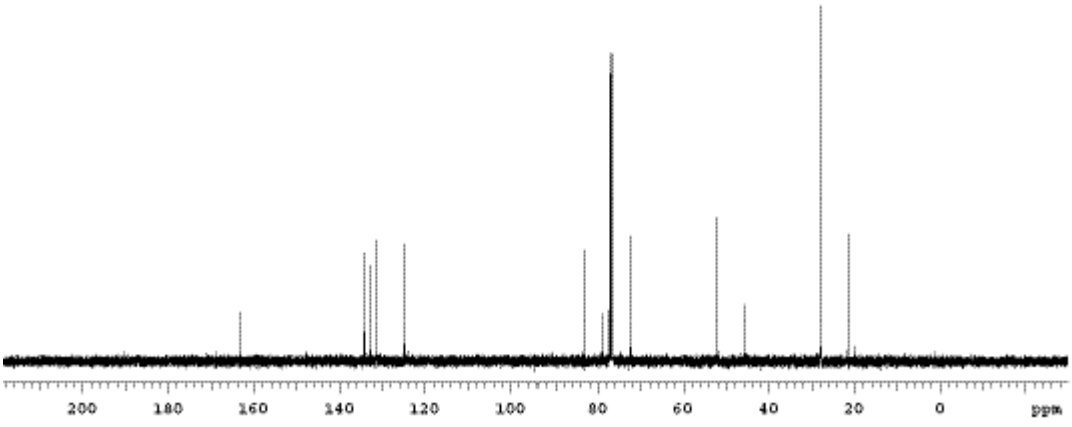
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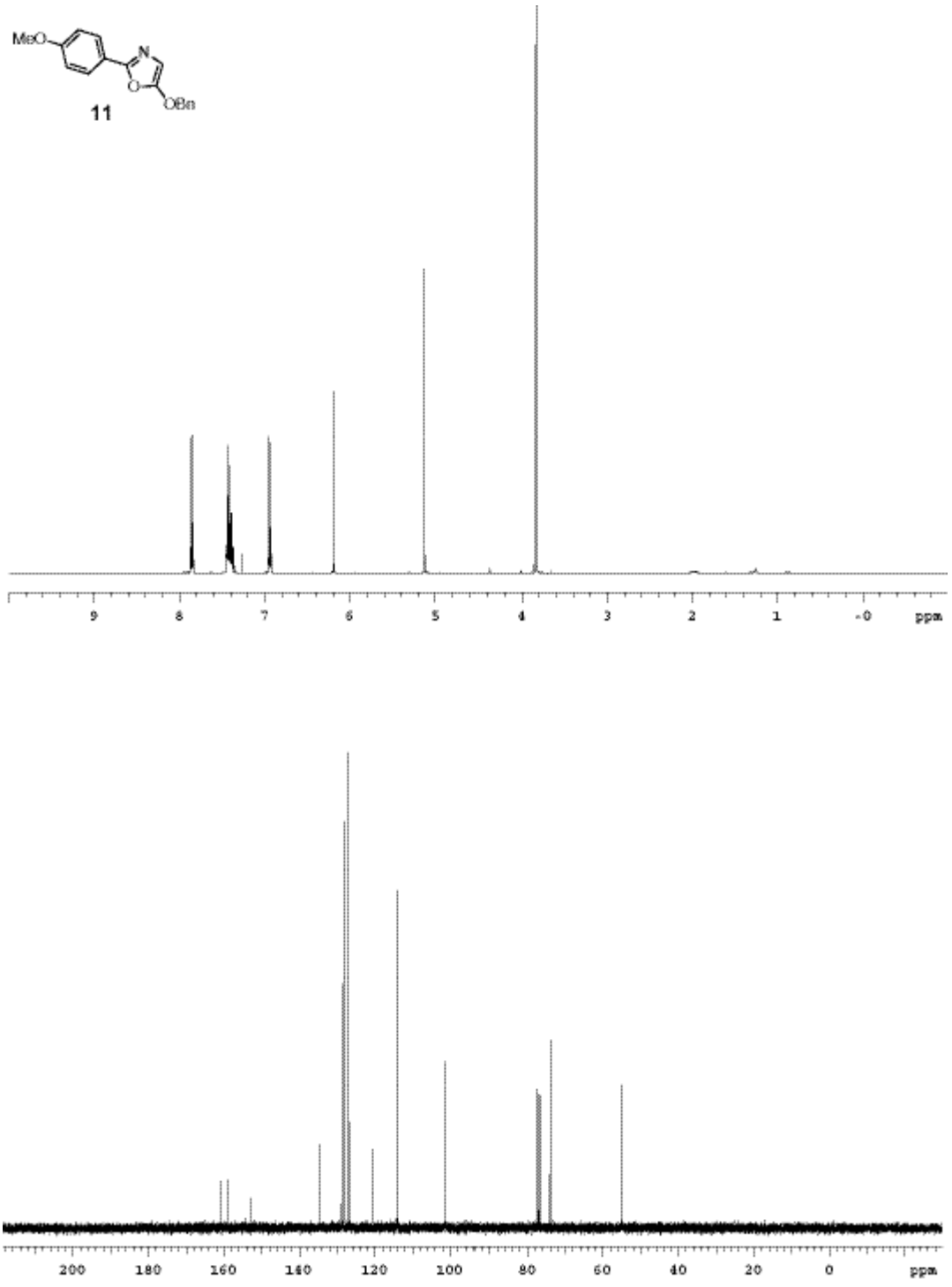
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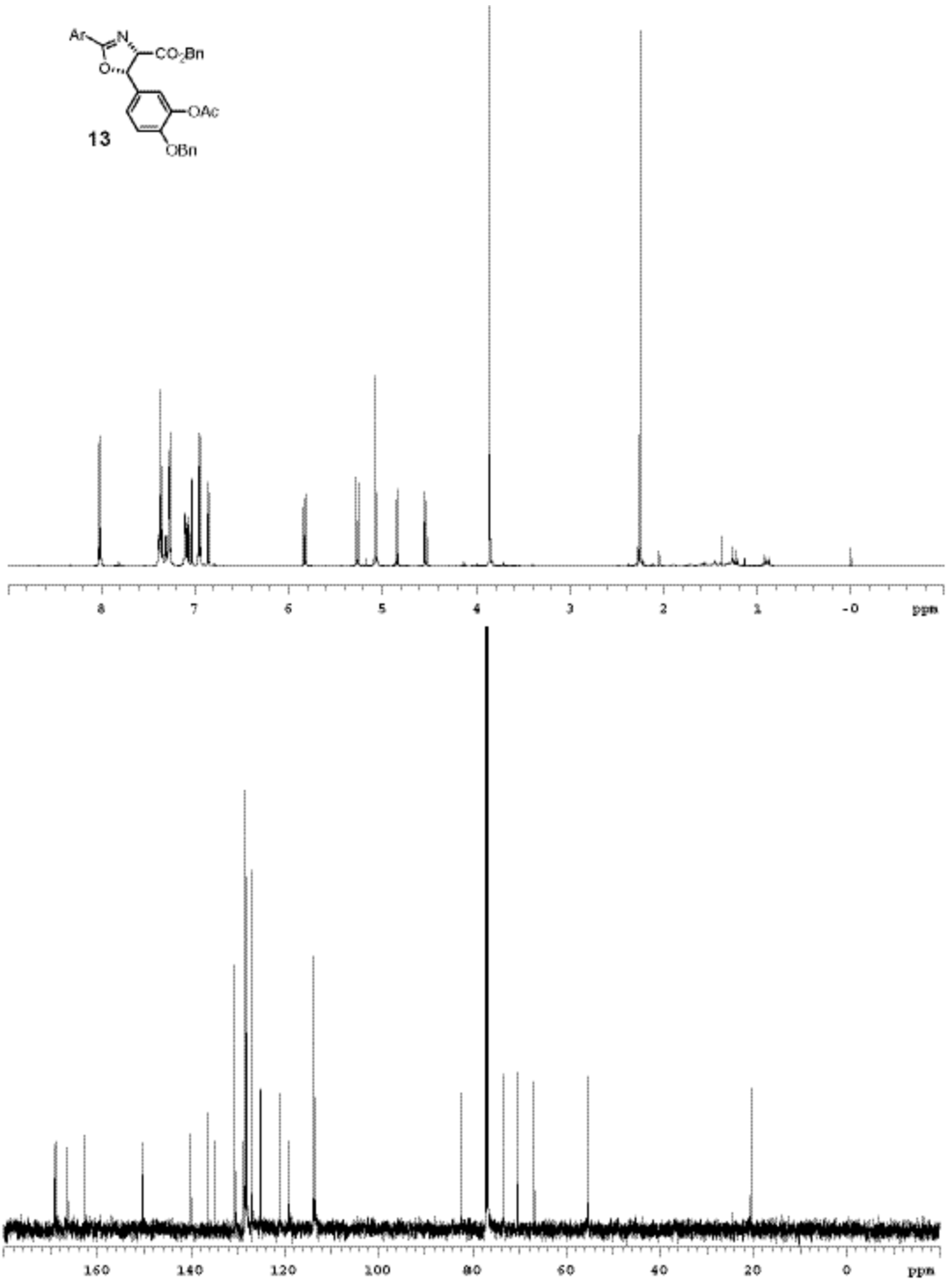
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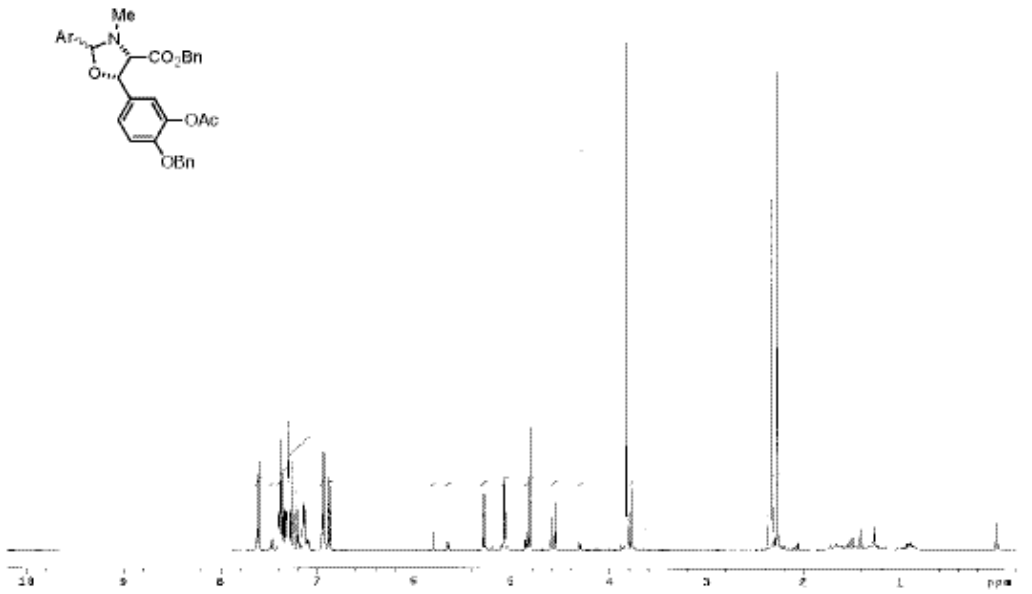
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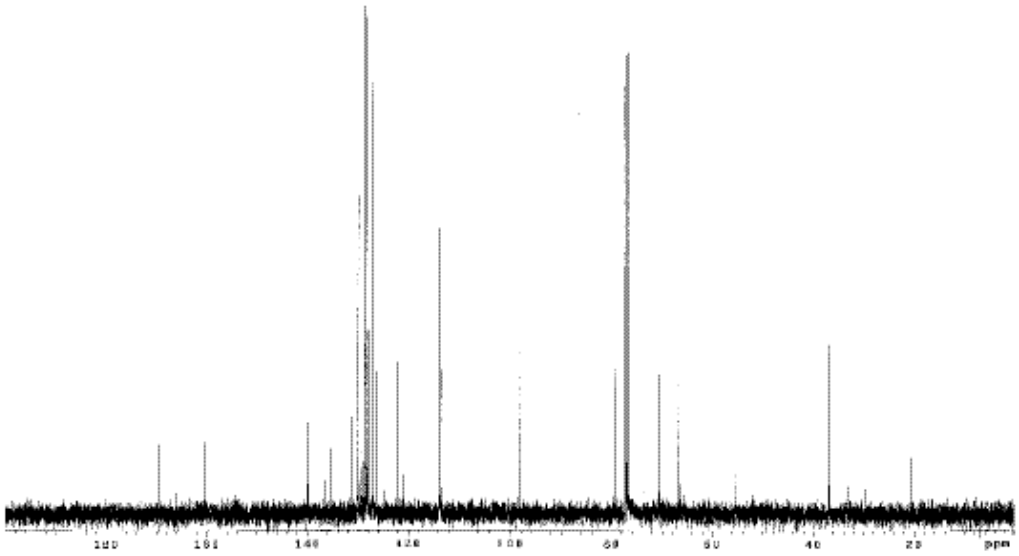
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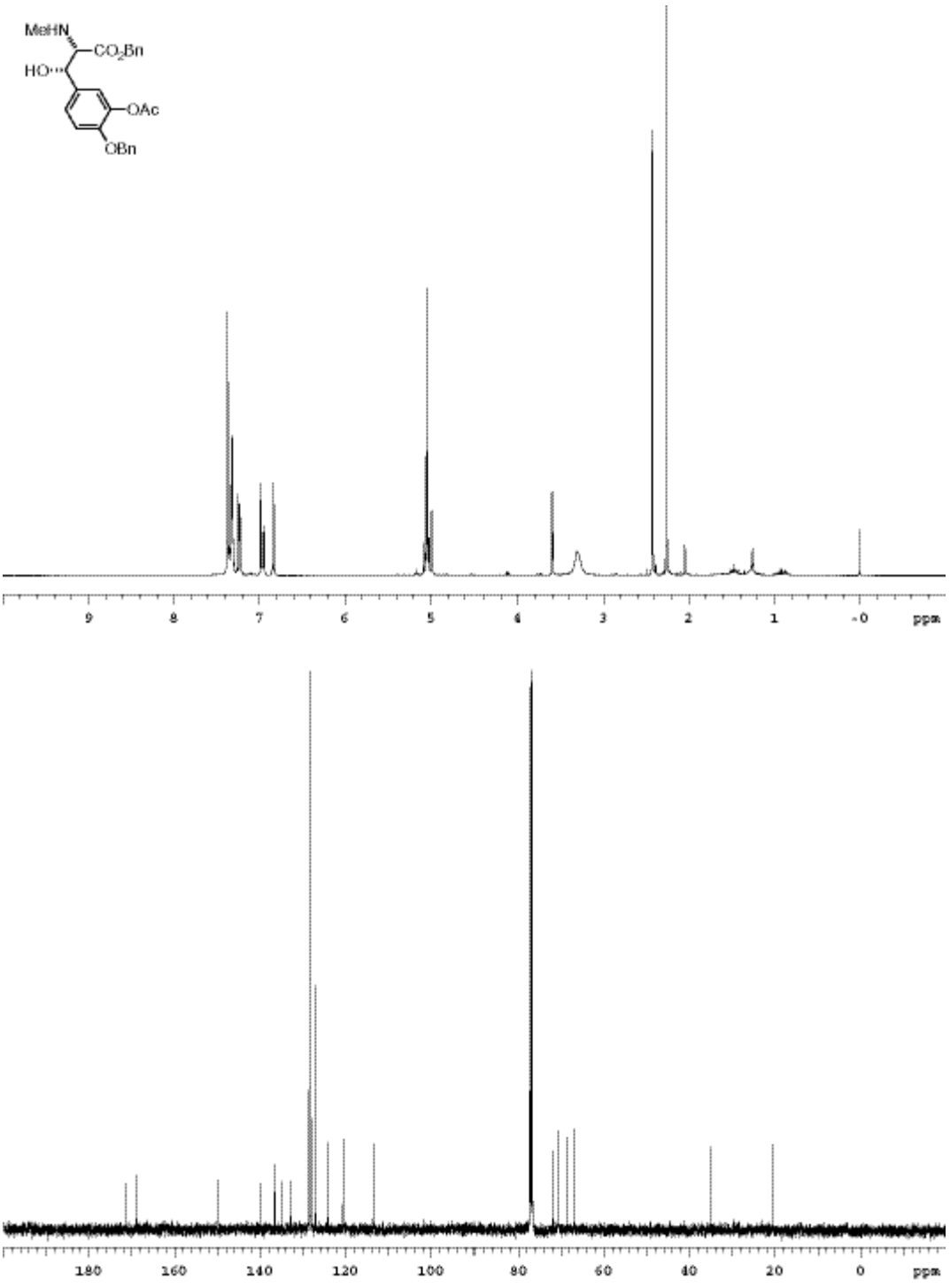
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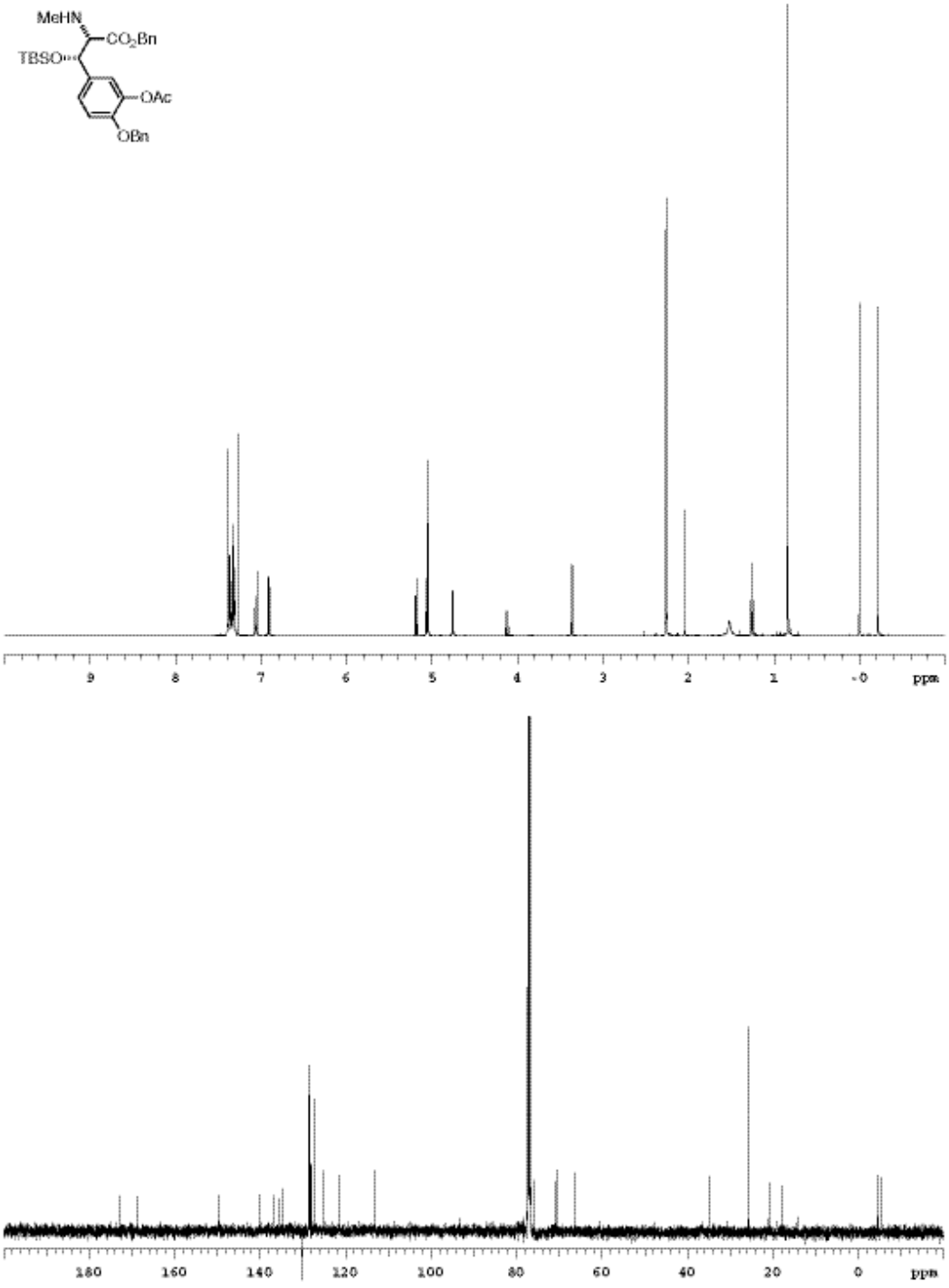
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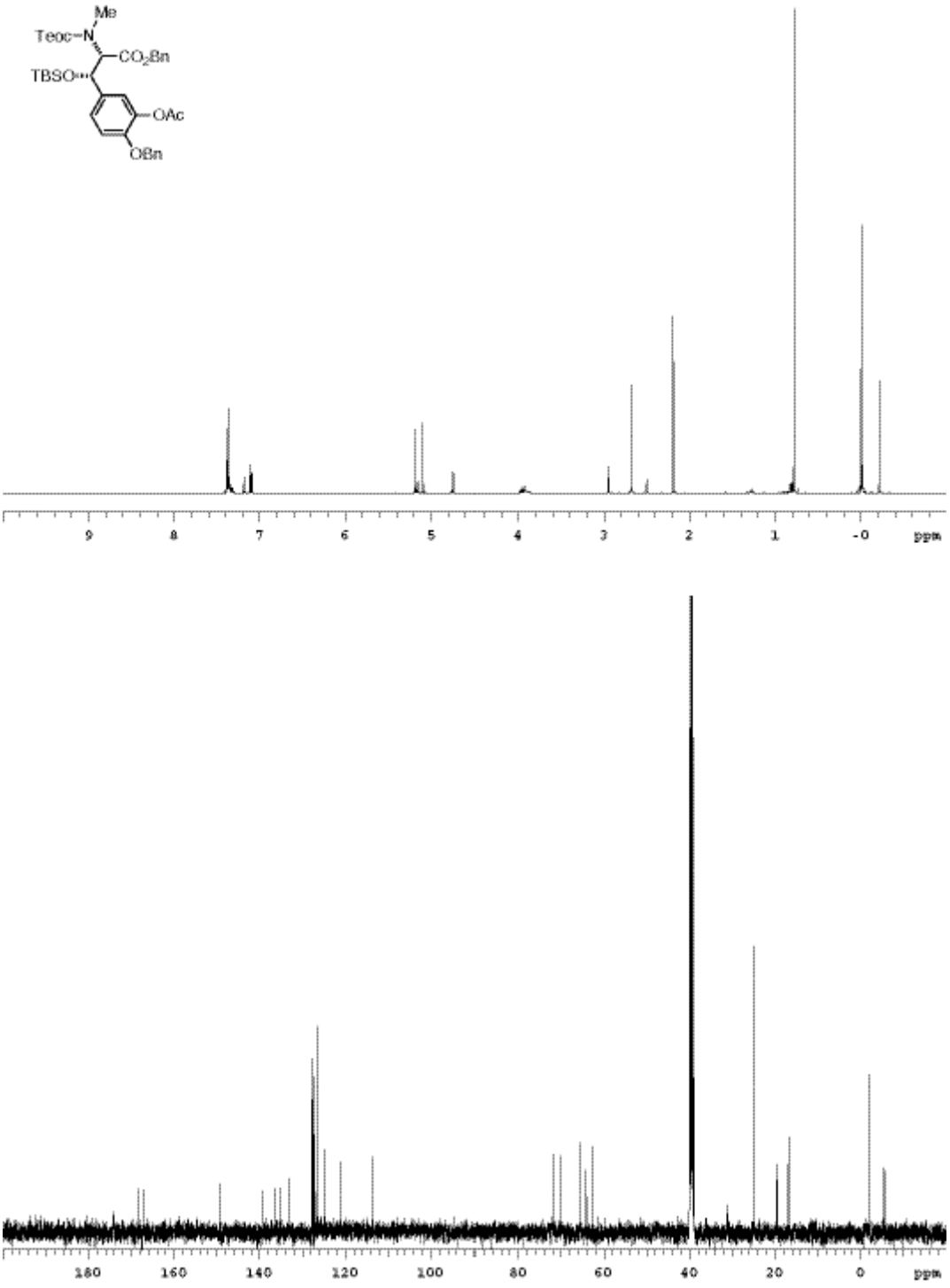
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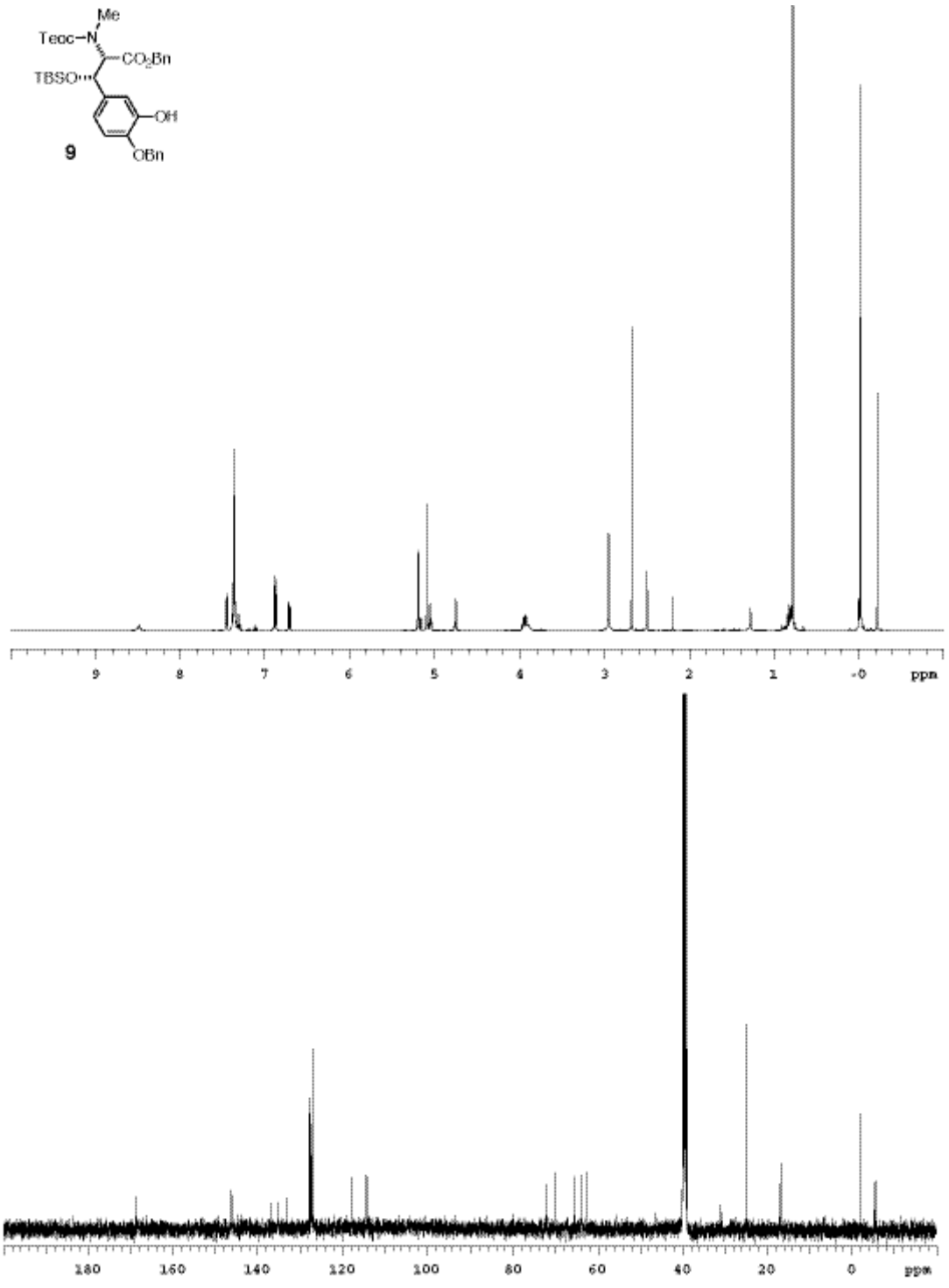
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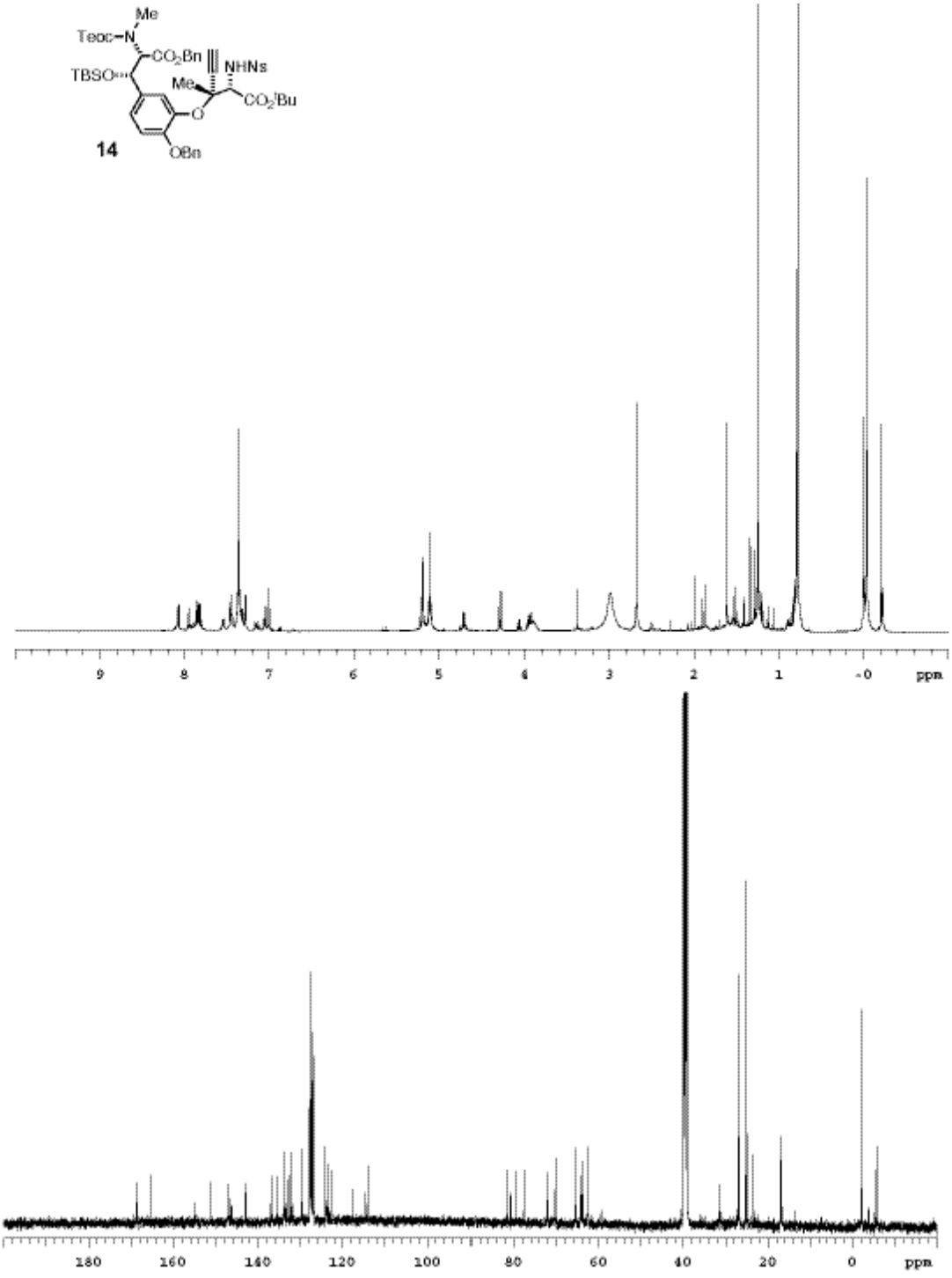
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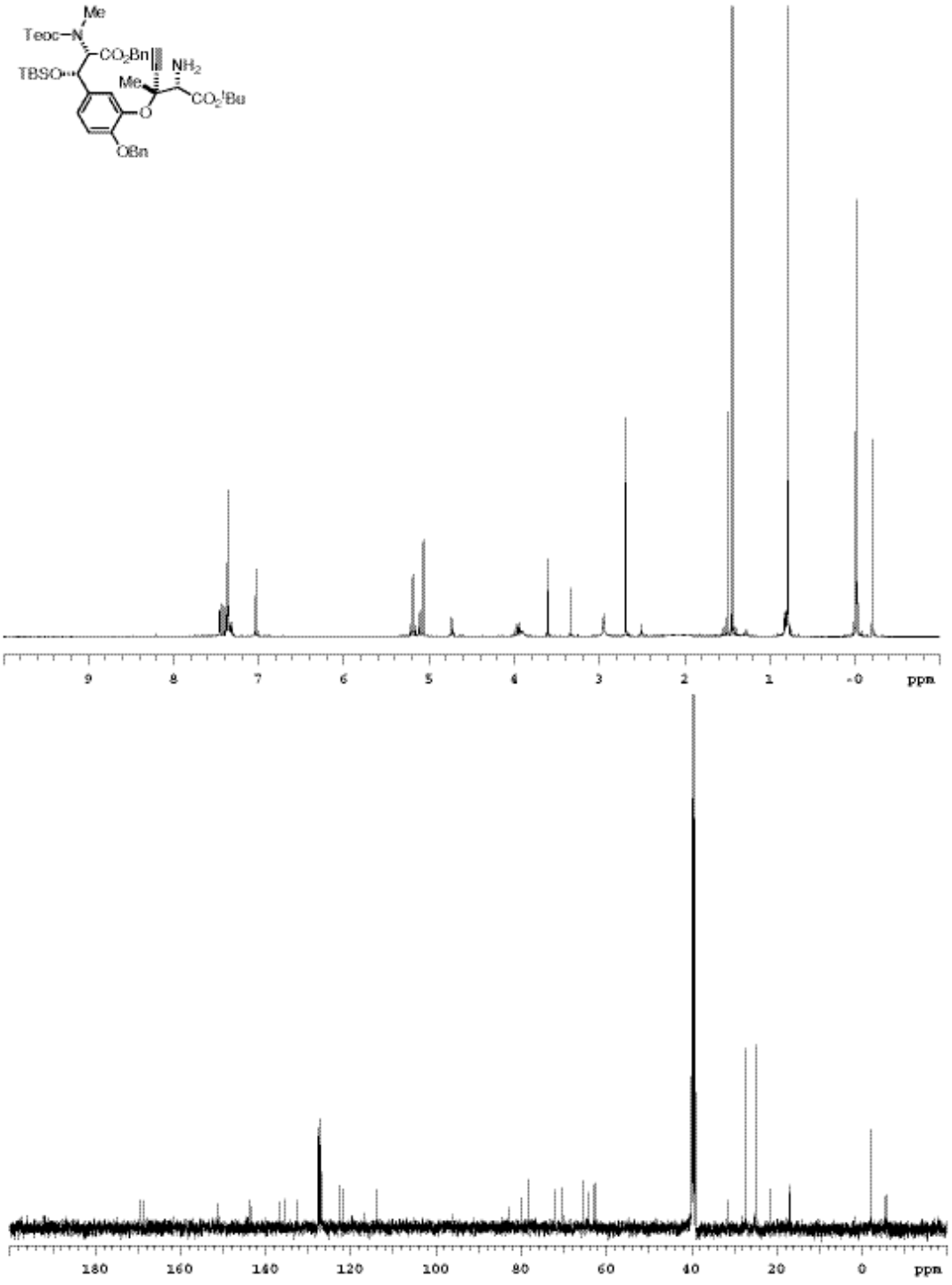
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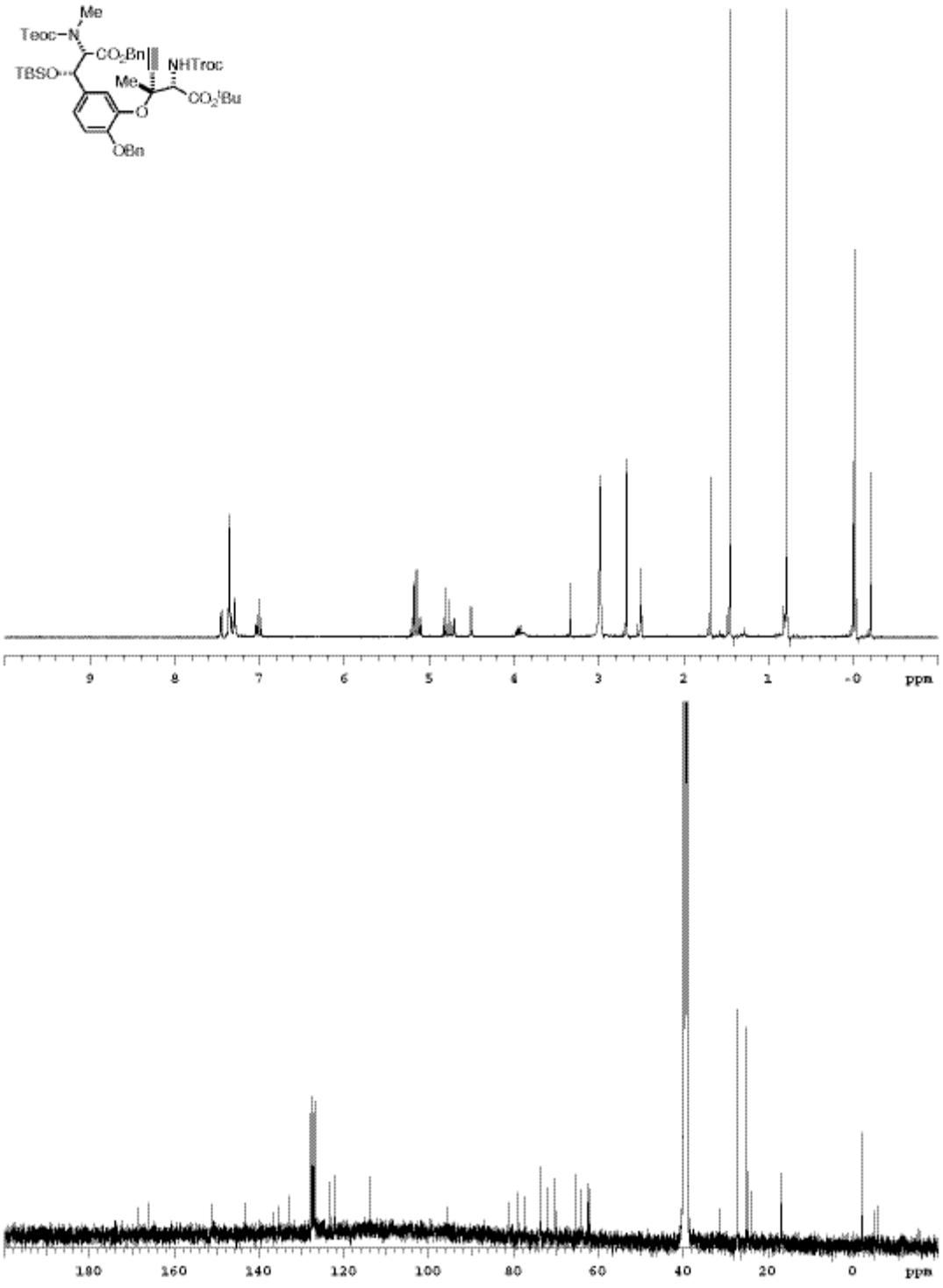
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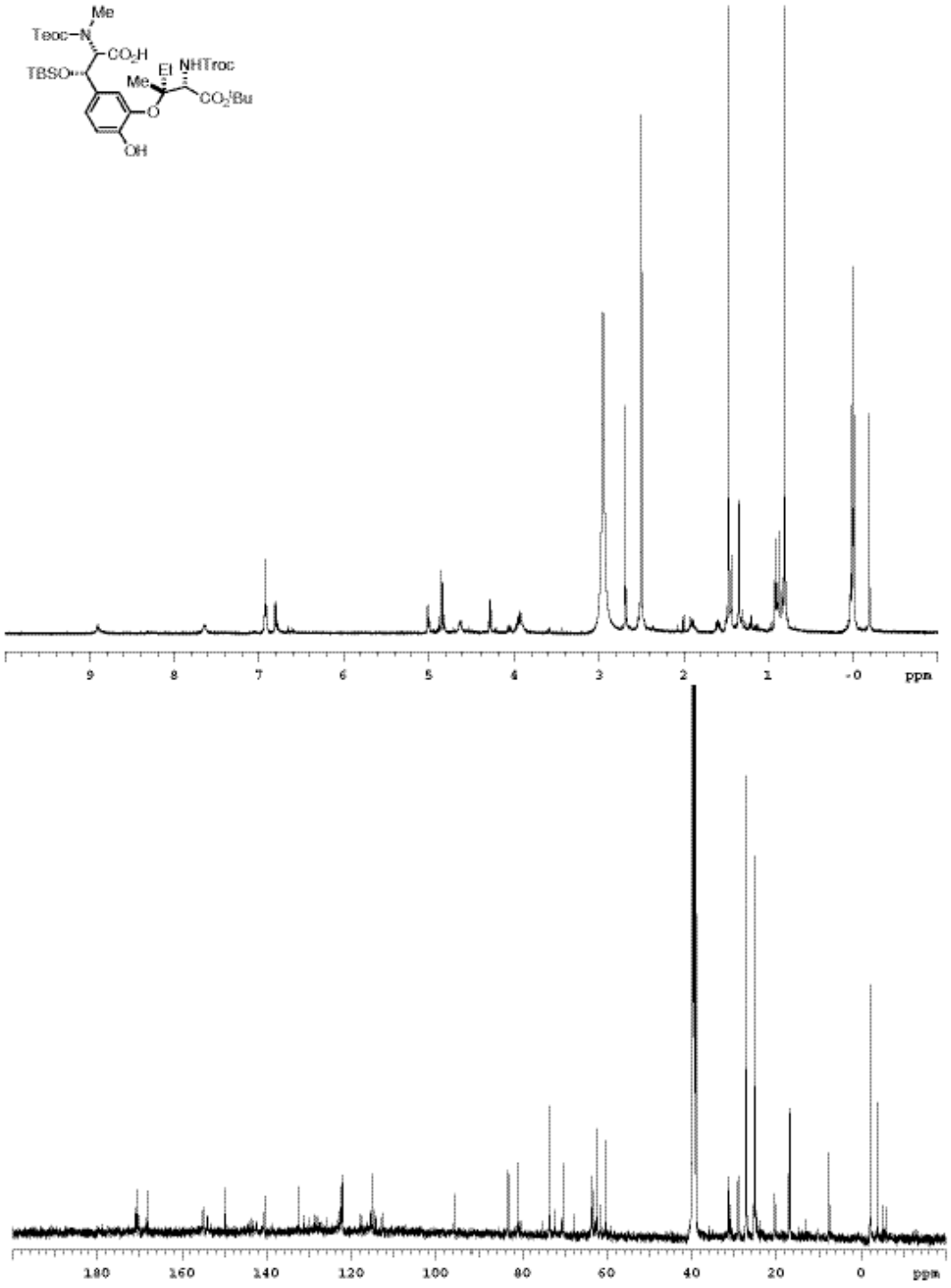
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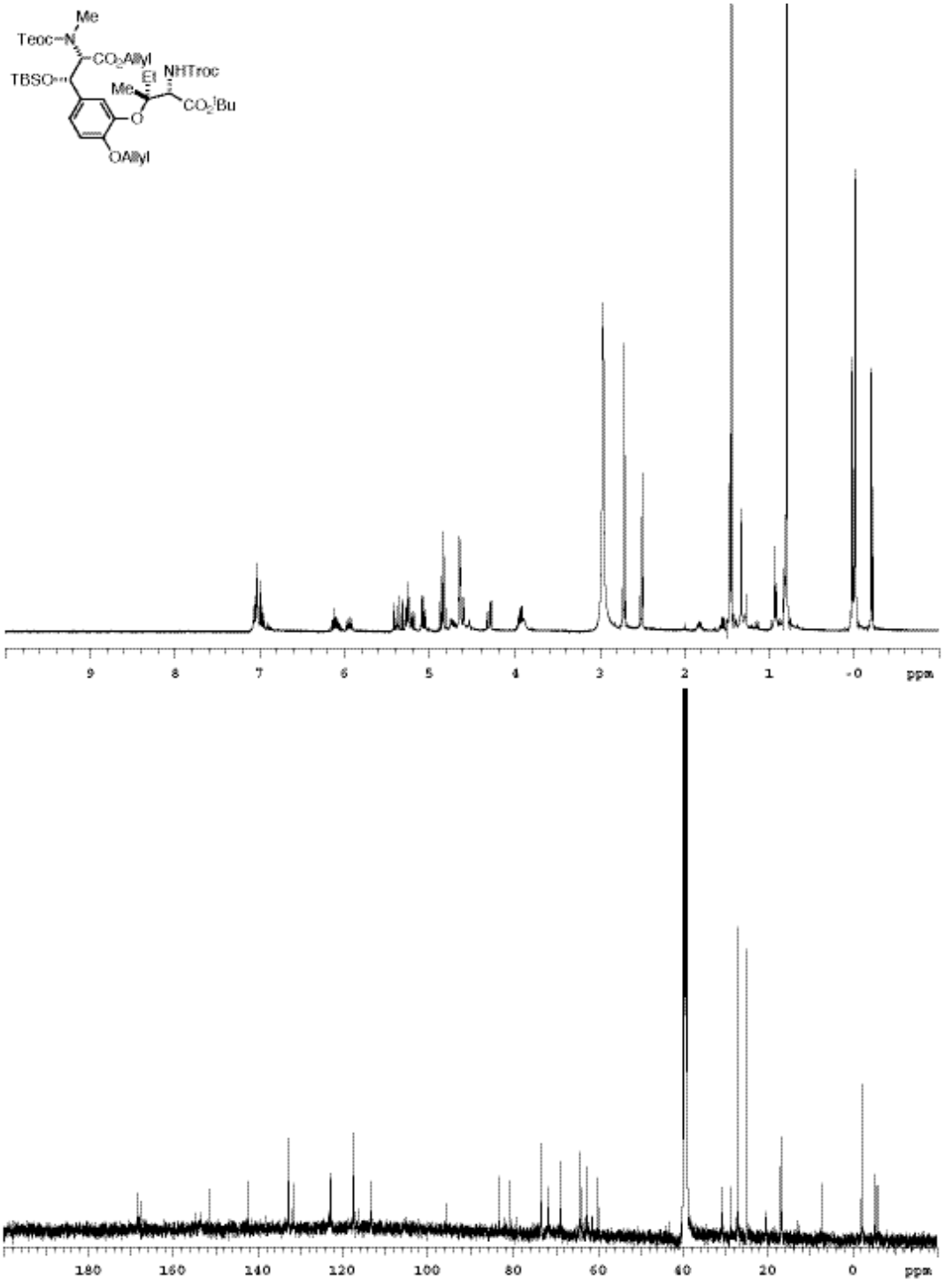
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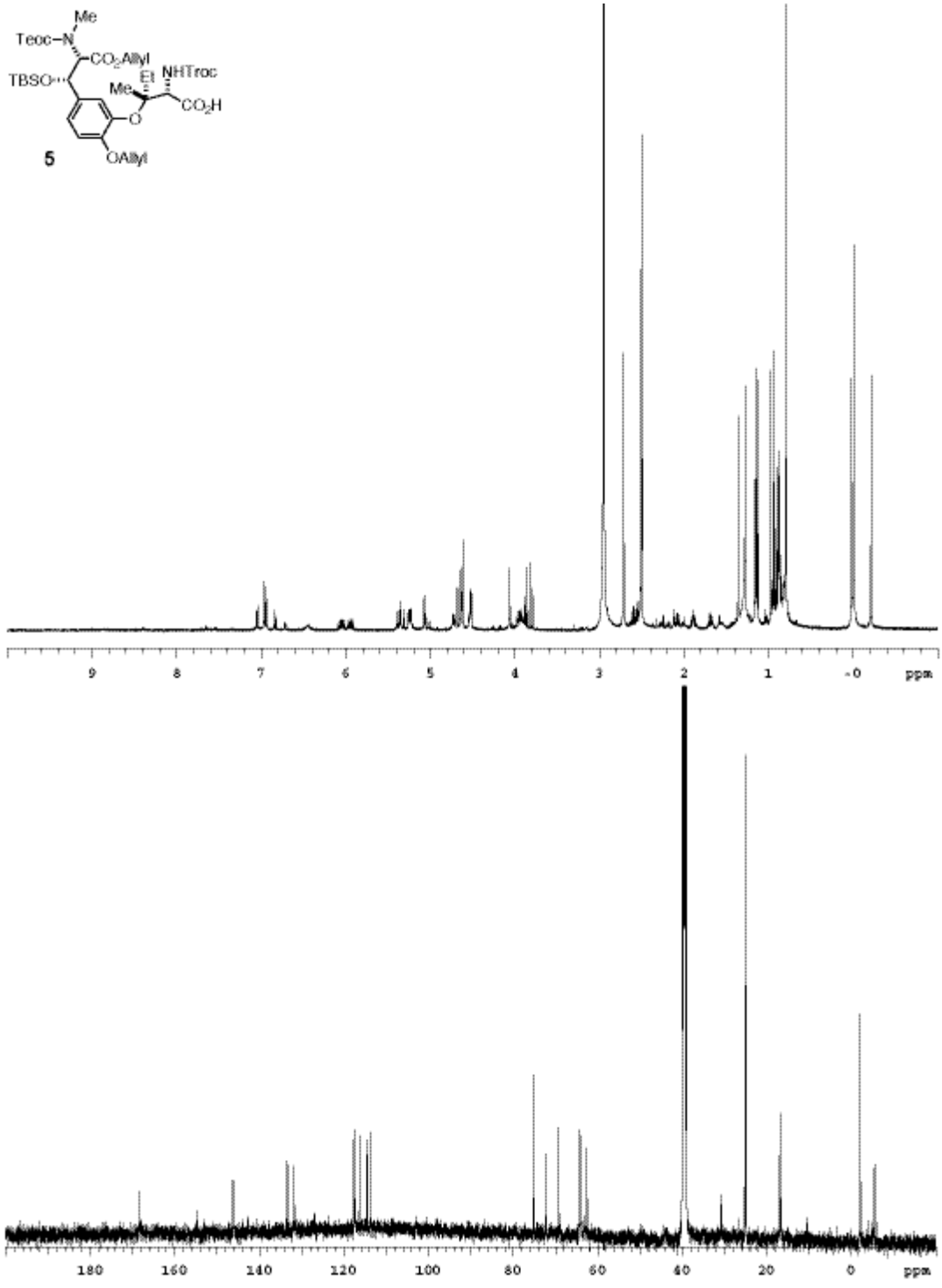
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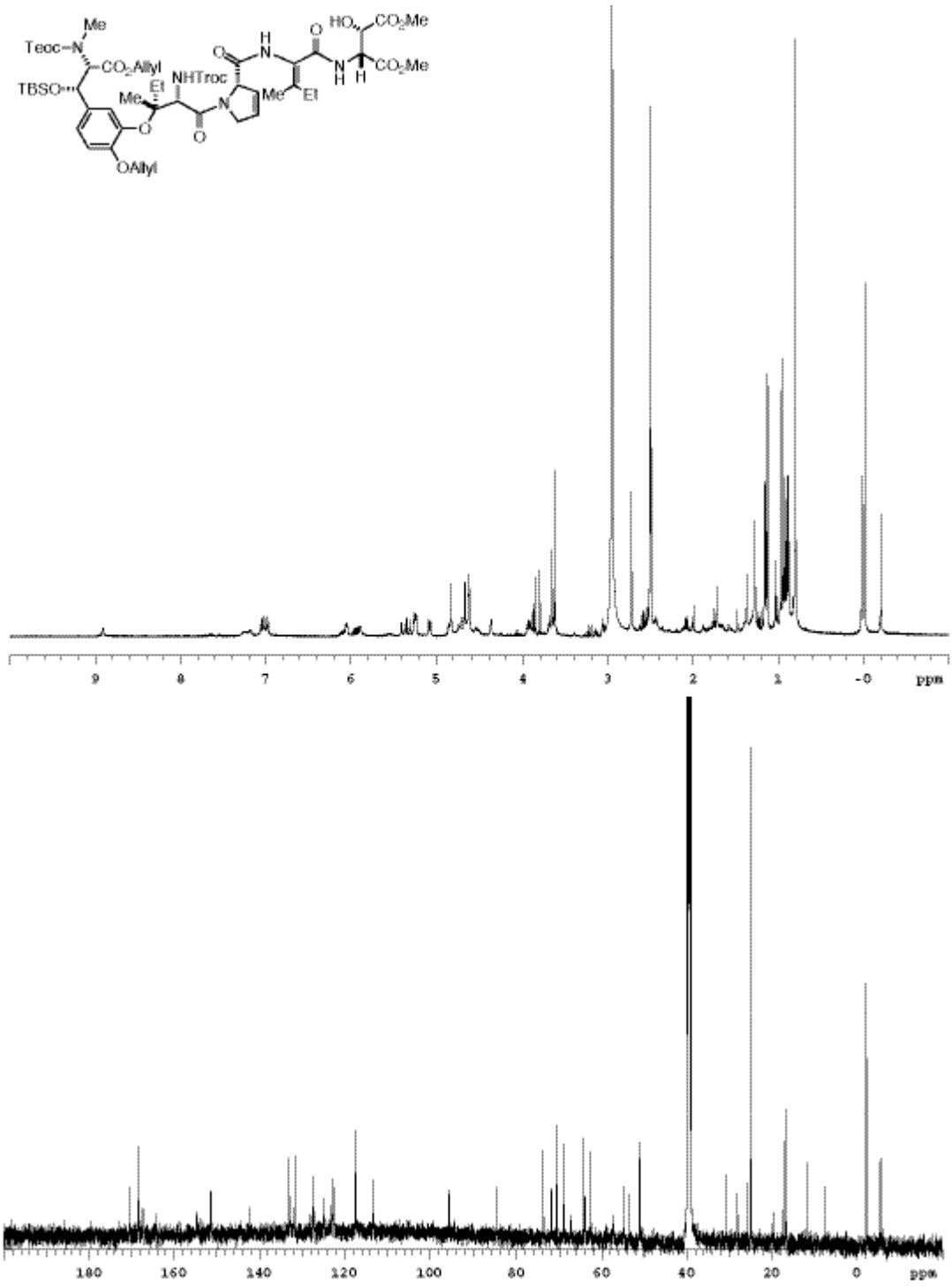
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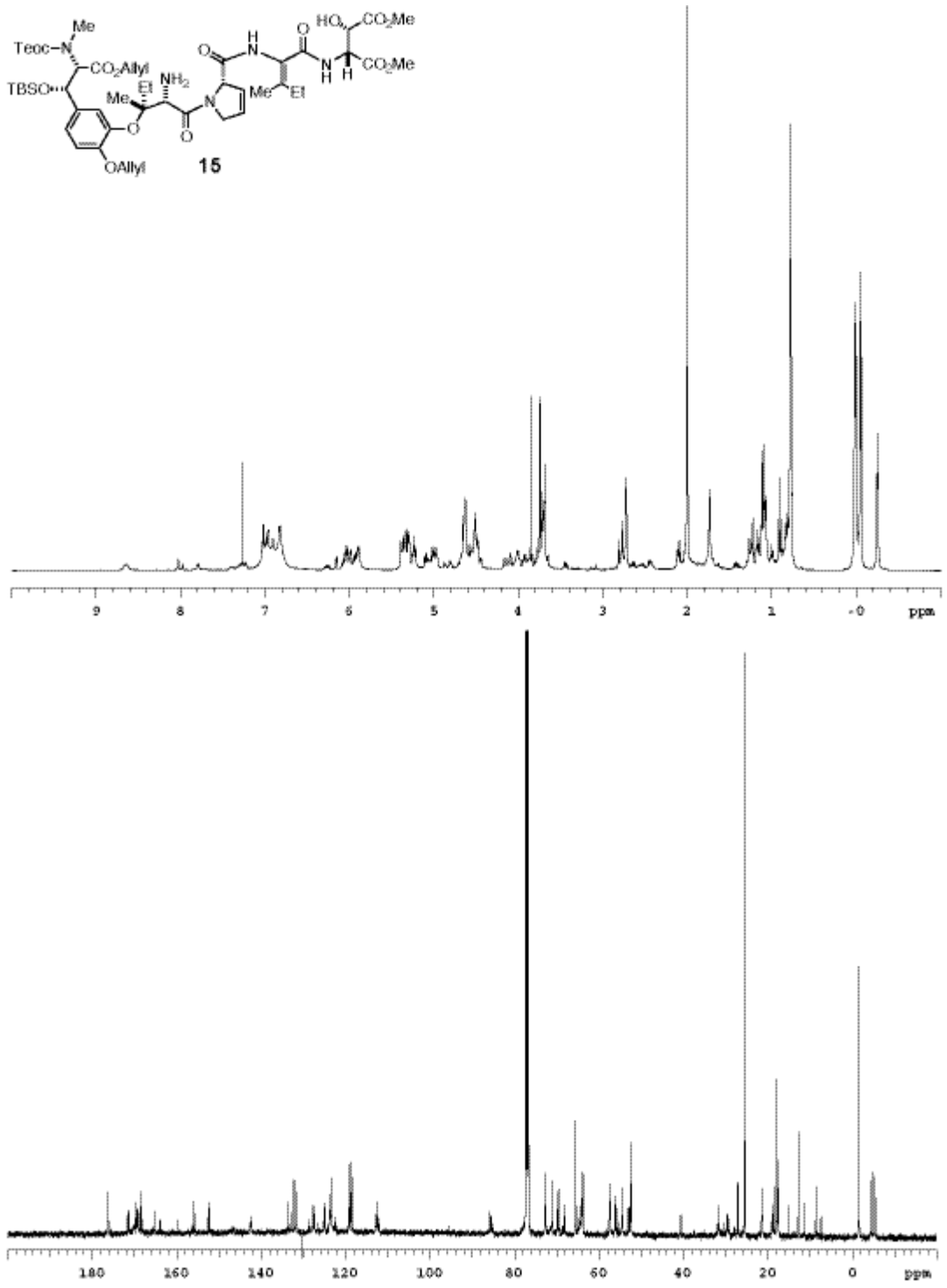
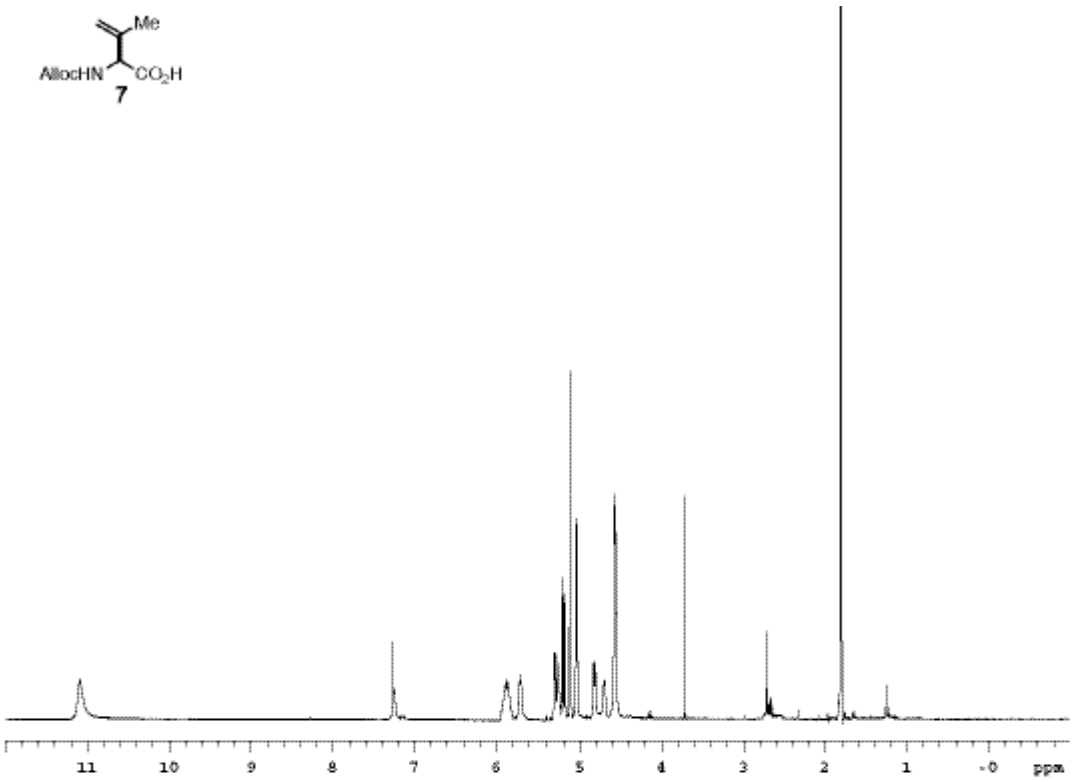
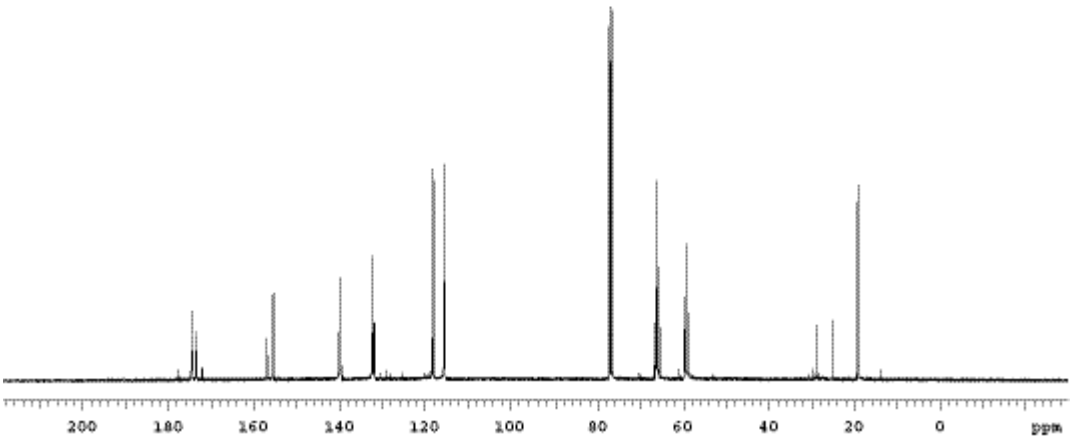

Me
Teoc–N
CO2Allyl
TBSO
Et
Me
NH2
O
O
OAllyl
N
O
H
N
O
H
N
HO
CO2Me
CO2Me
Me
Et
15
9
8
7
6
5
4
3
2
1
0
ppm
180
160
140
120
100
80
60
40
20
0
ppm


Me
AllocHN
CO2H
7
11
10
9
8
7
6
5
4
3
2
1
-0
ppm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180
160
140
120
100
80
60
40
20
0
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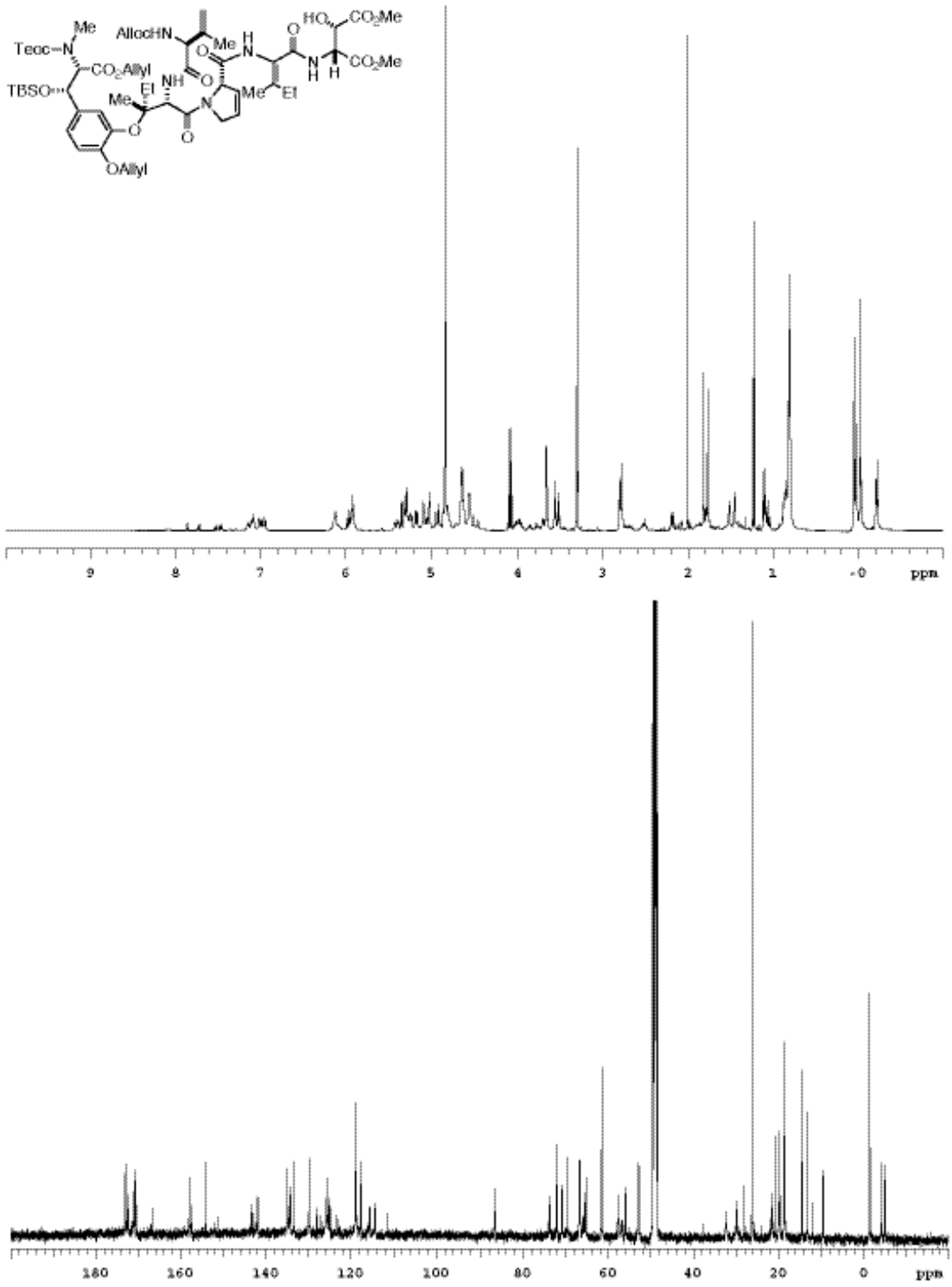
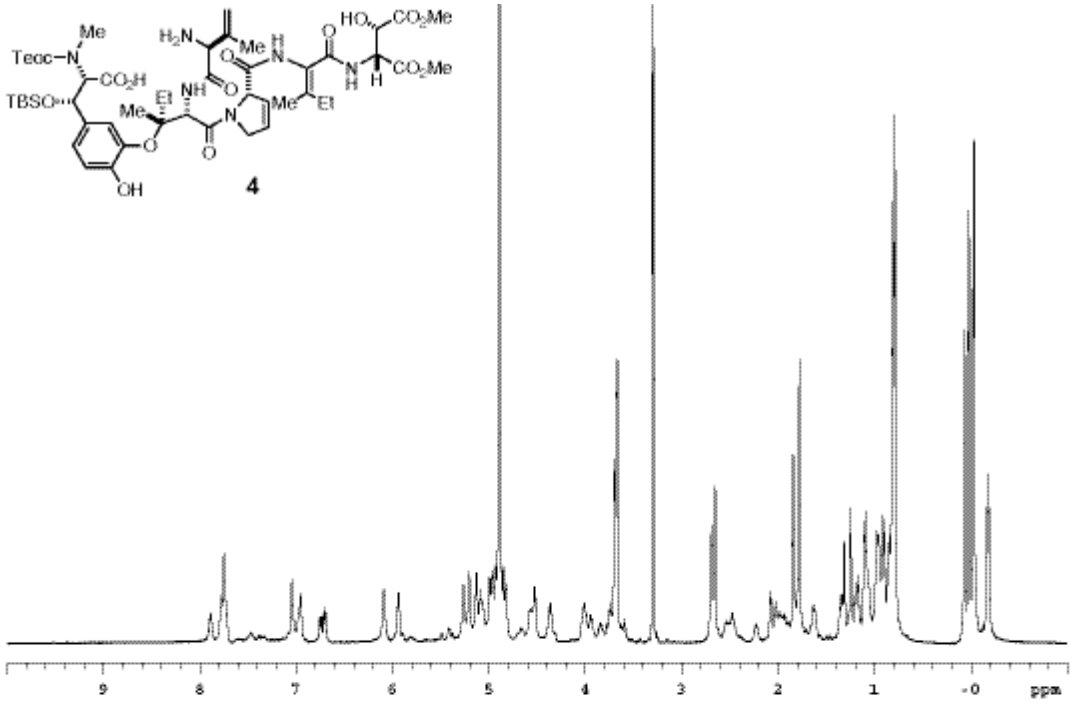
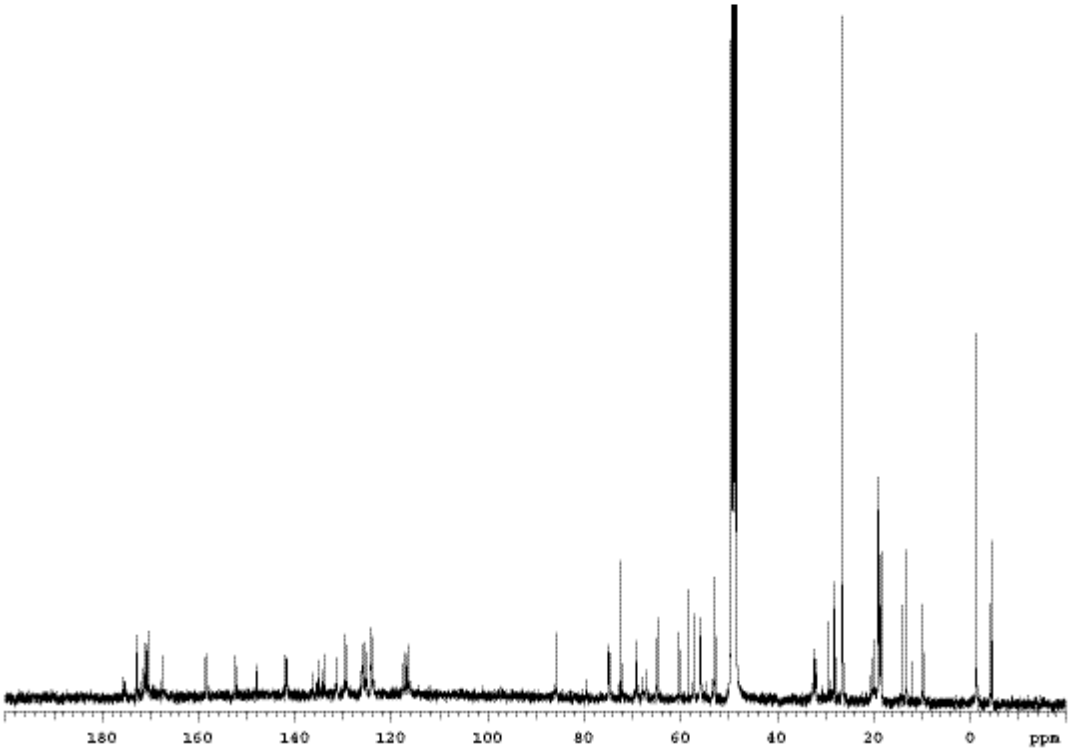
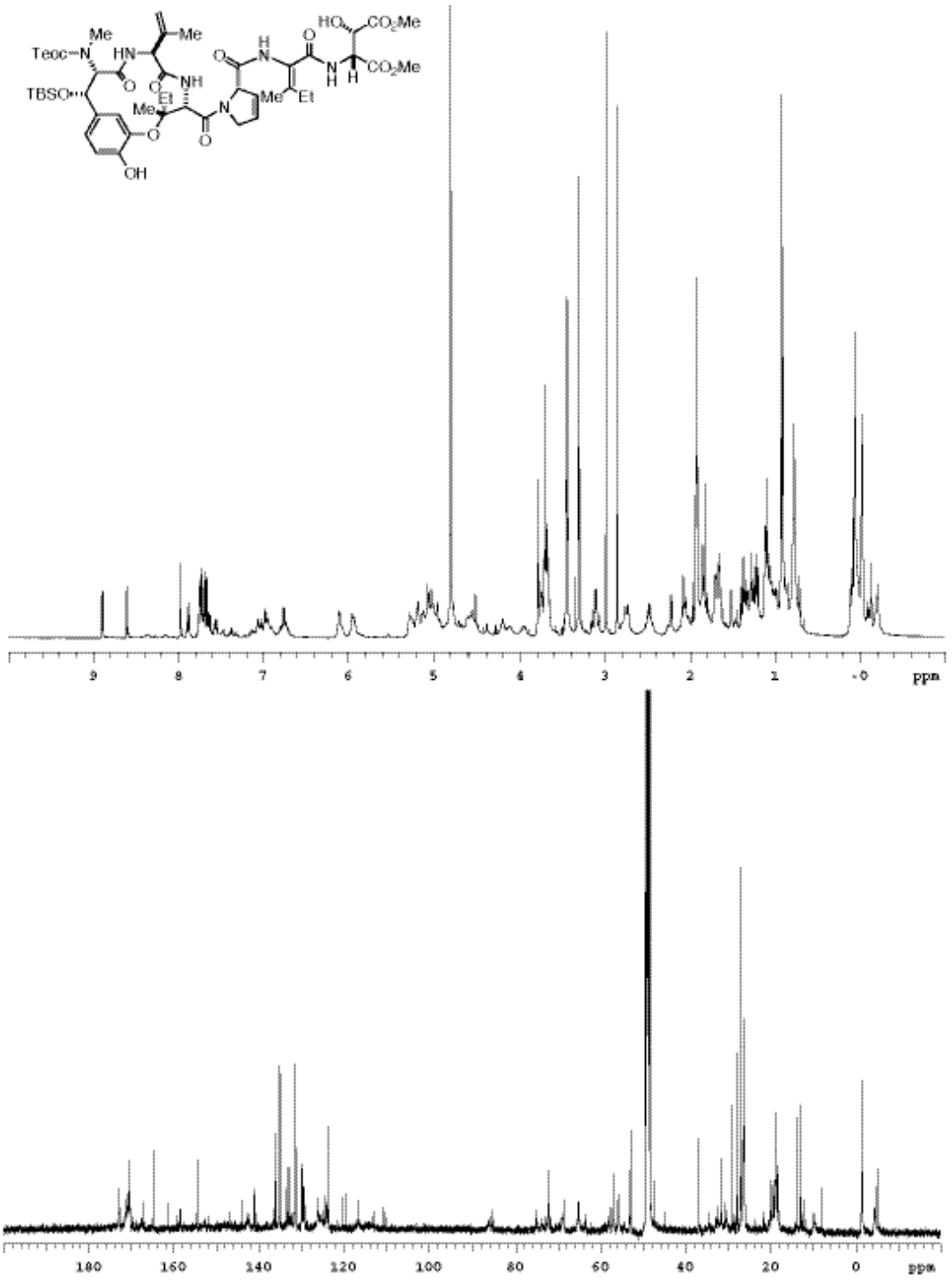
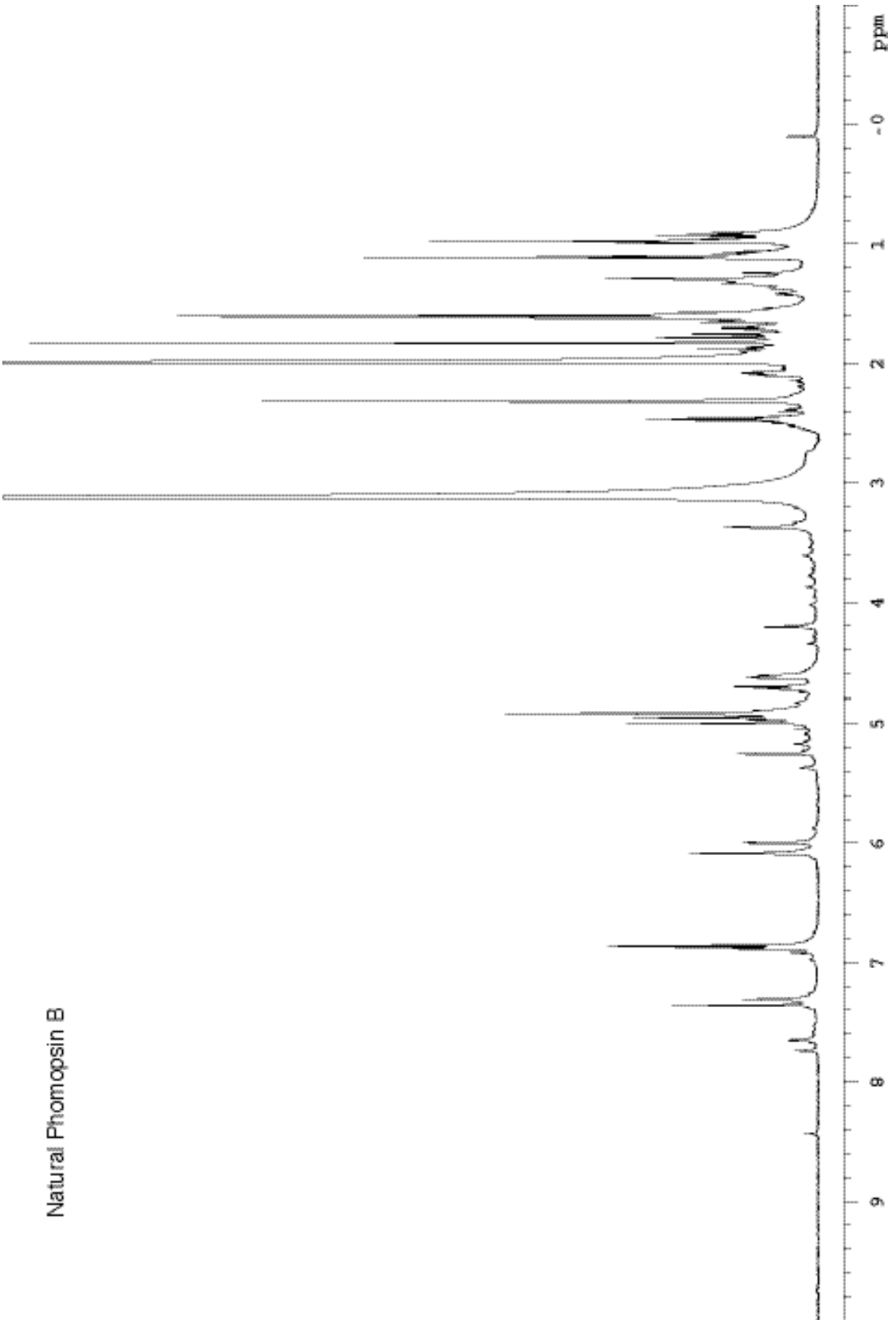
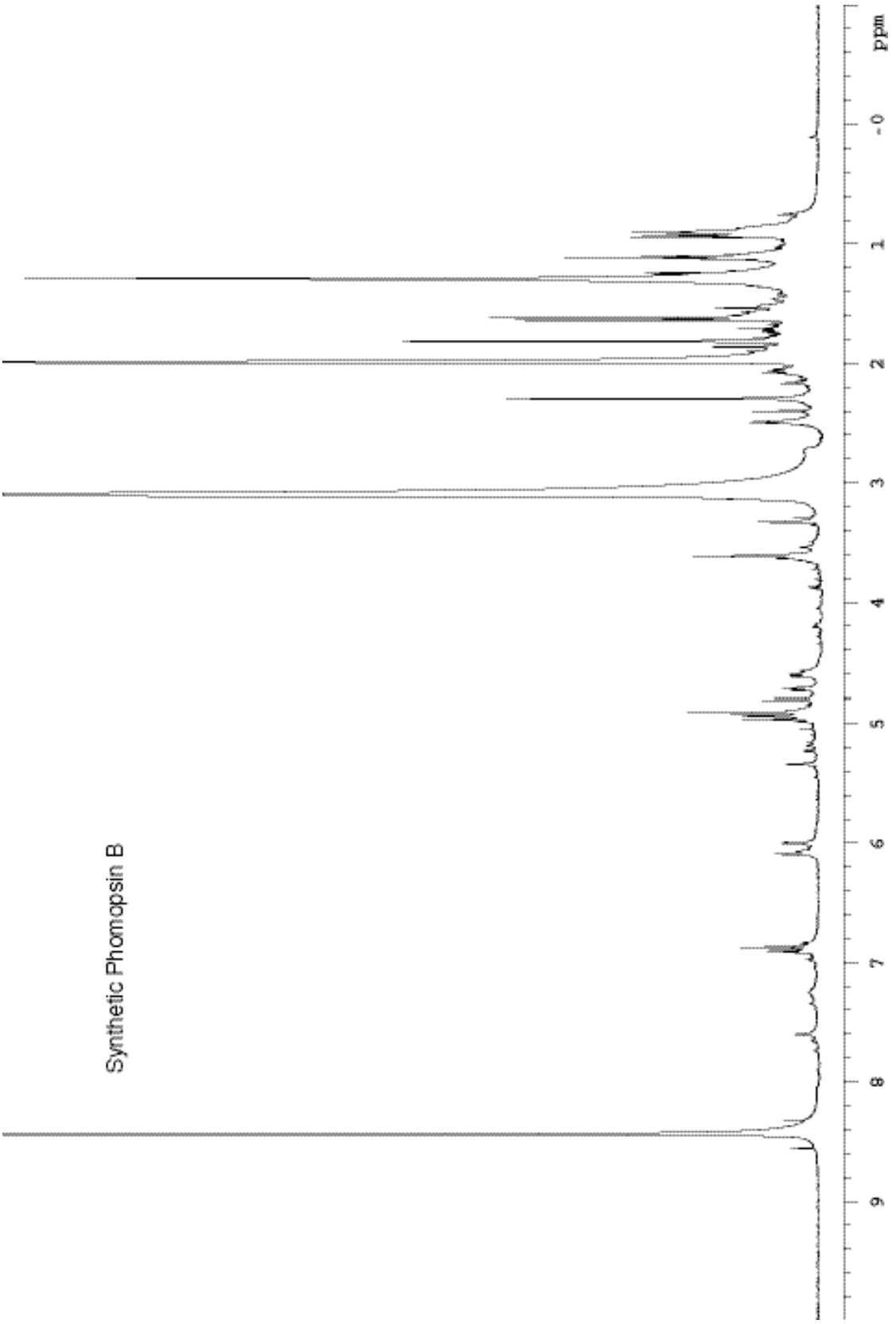

Me
Teoc
N
CO2Allyl
TBSO
AllocHN
O
Me
NH
Et
Me
O
N
O
Me
Et
HO
CO2Me
H
N
N
H
H
CO2Me
O
O
OAllyl
9
8
7
6
5
4
3
2
1
-0
ppm
180
160
140
120
100
80
60
40
20
0
ppm

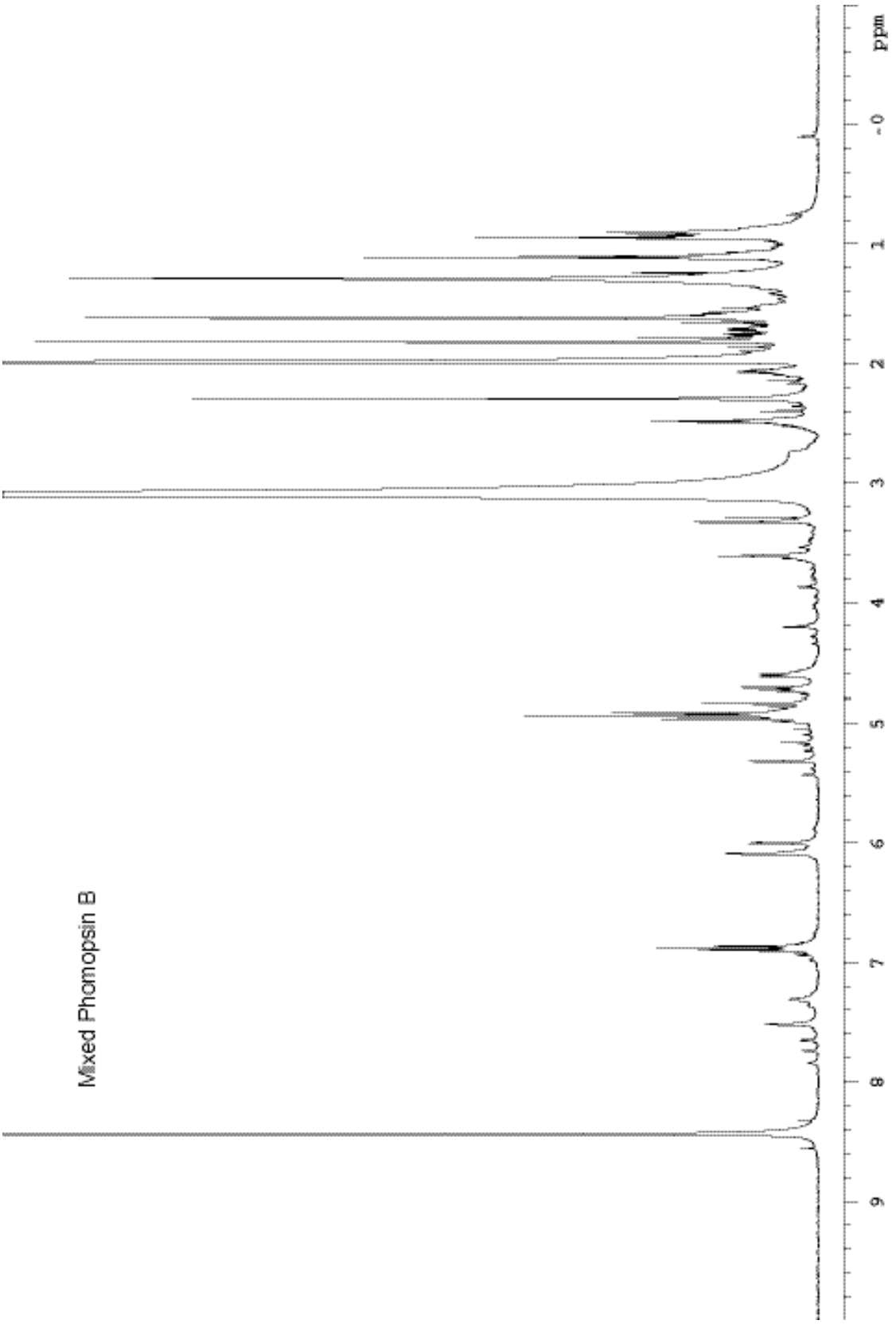

Me
Teoc–N
CO2H
TBSO
Et
Me
O
OH
NH
O
O
N
Me
Et
H2N
Me
O
N
H
O
HO
CO2Me
N
H
CO2Me
4
9
8
7
6
5
4
3
2
1
-0
ppm

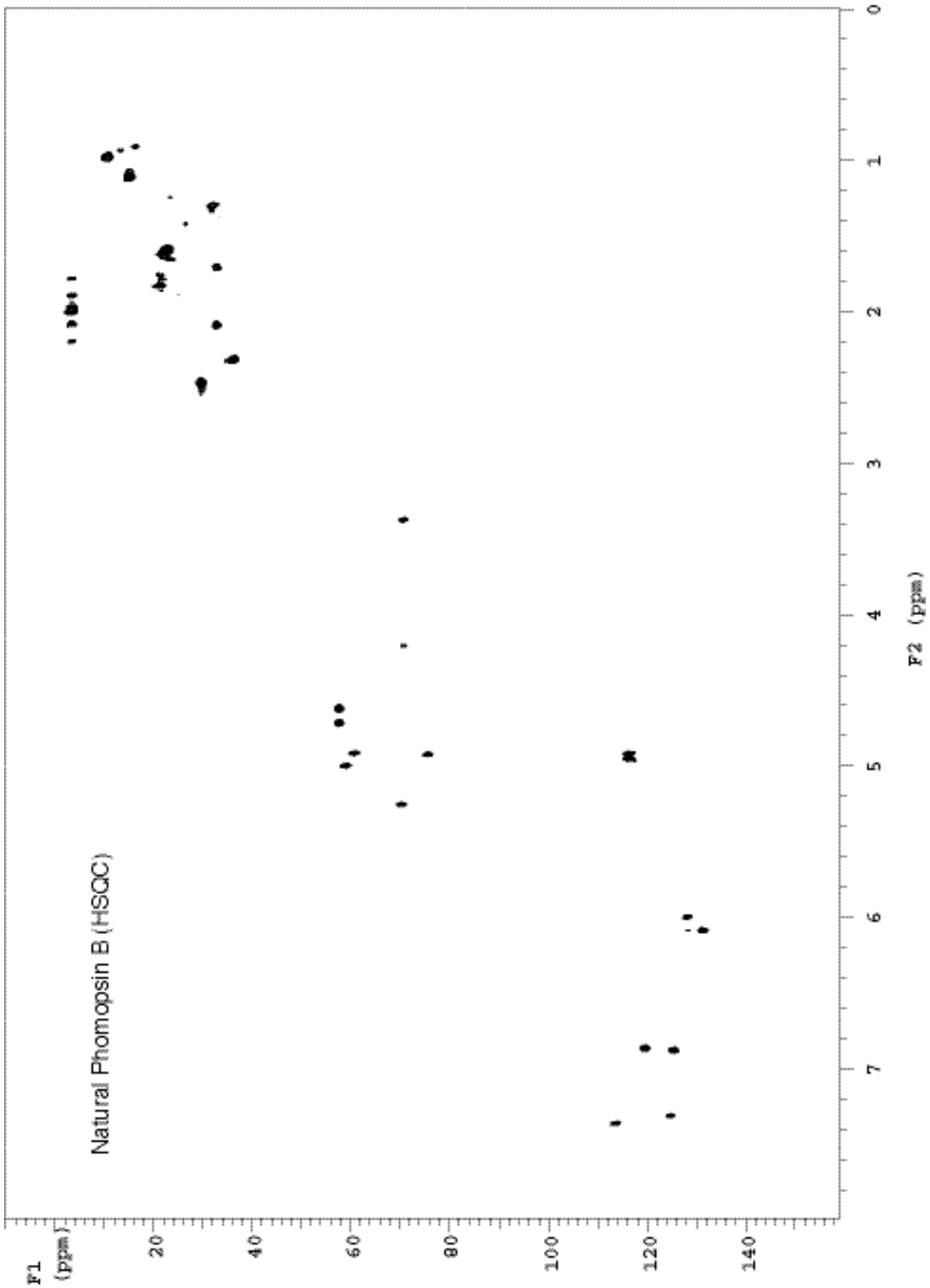

180
160
140
120
100
80
60
40
20
0
ppm

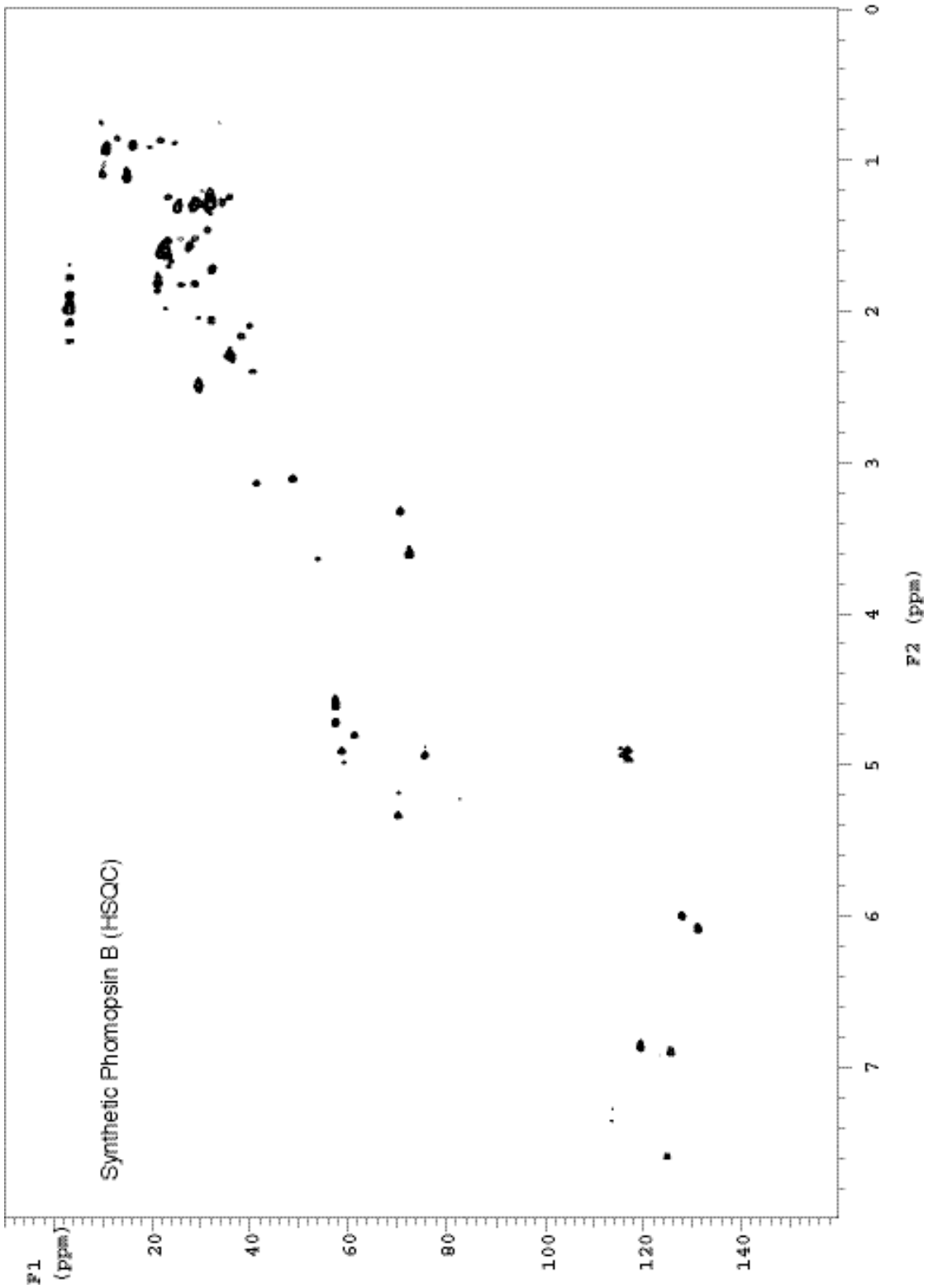

Me
Me
Teoc
N
HN
O
O
NH
TBSO
Et
Me
O
O
OH
N
H
O
N
H
Me
Et
HO
CO2Me
CO2Me
9
8
7
6
5
4
3
2
1
0
ppm
180
160
140
120
100
80
60
40
20
0
ppm

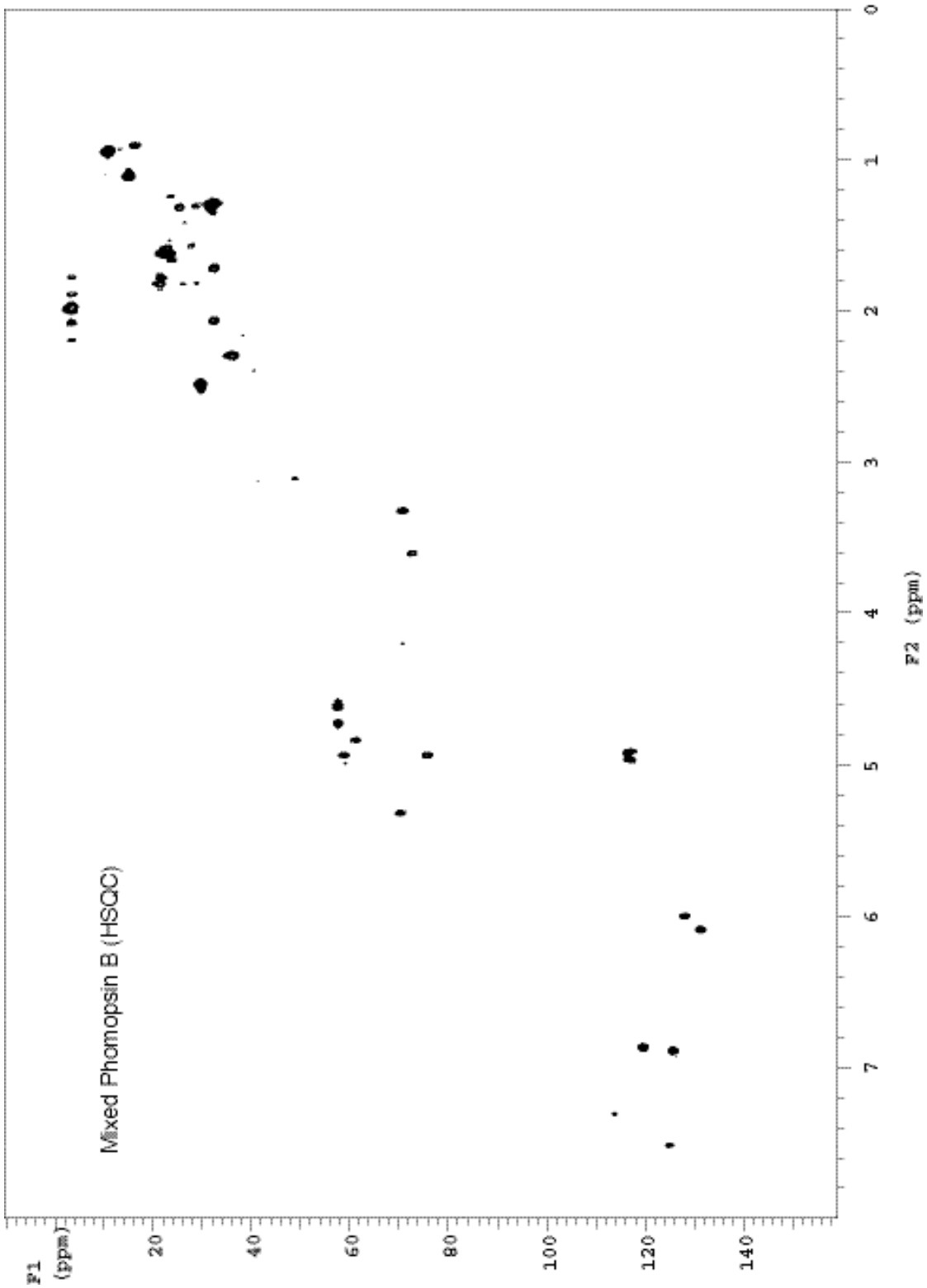

Natural Phomopsin B
ppm
9
8
7
6
5
4
3
2
1
0

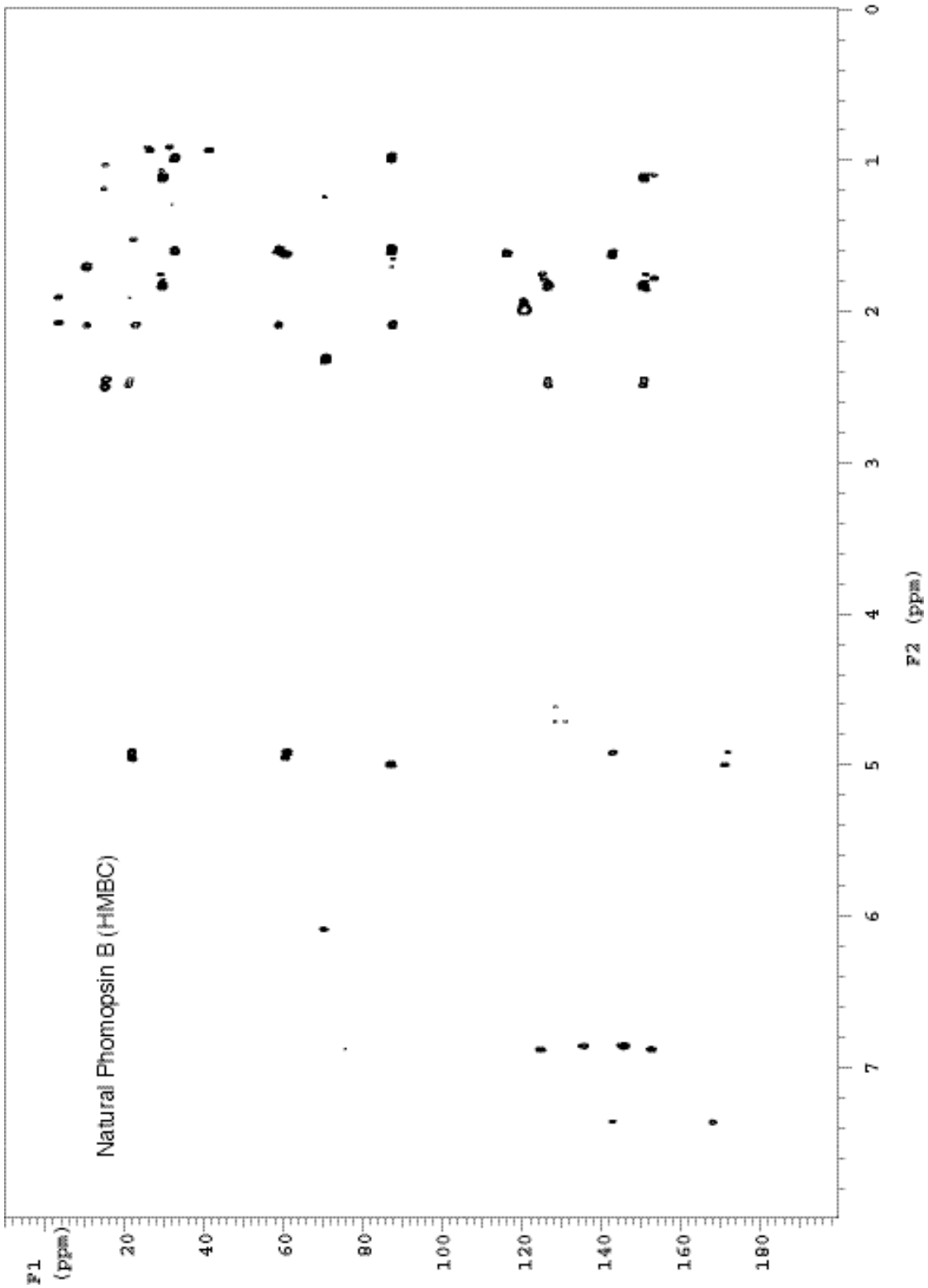

Synthetic Phomopsin B
ppm
9
8
7
6
5
4
3
2
1
0

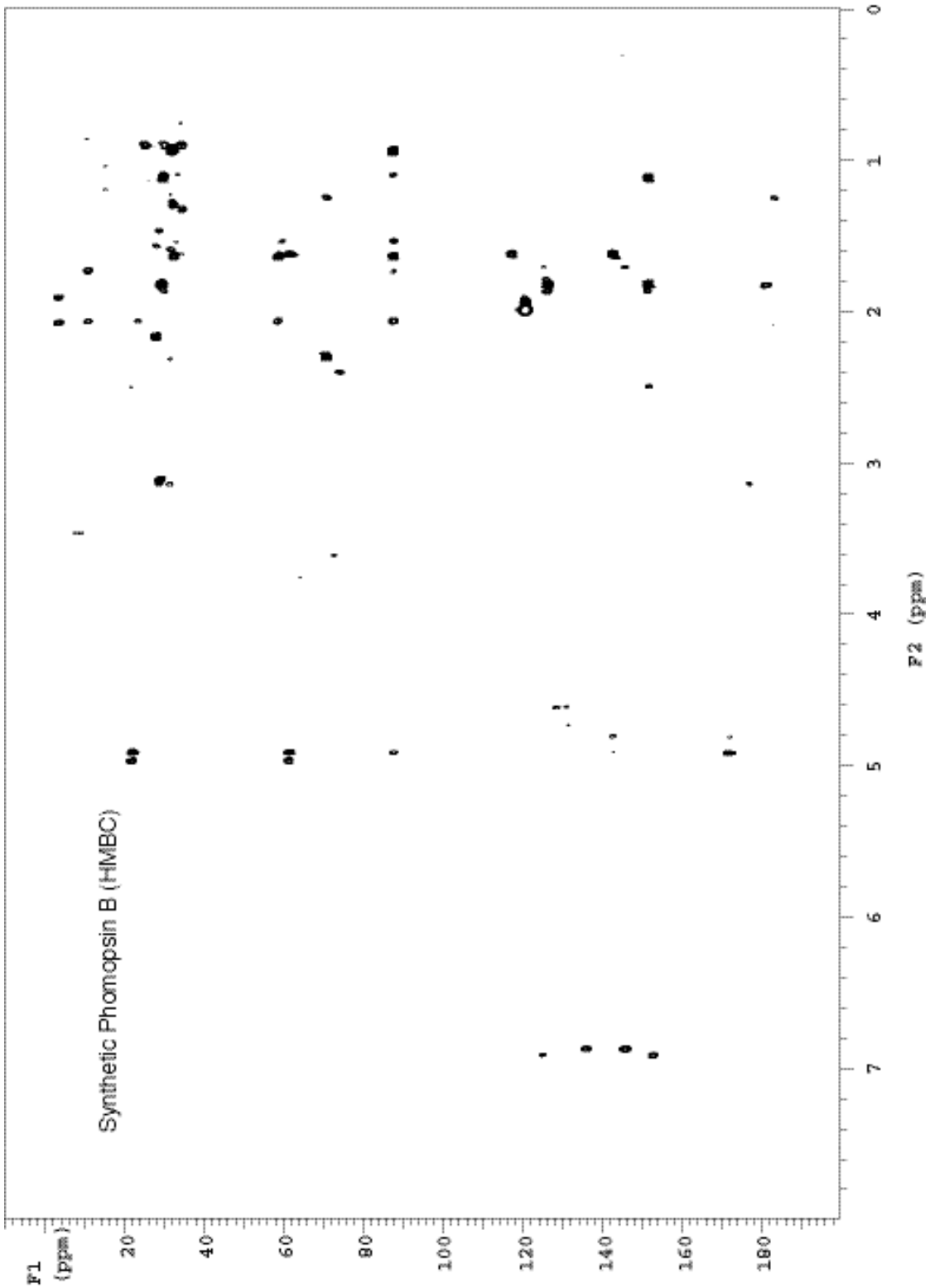

Mixed Phomopsin B
ppm
9
8
7
6
5
4
3
2
1
0

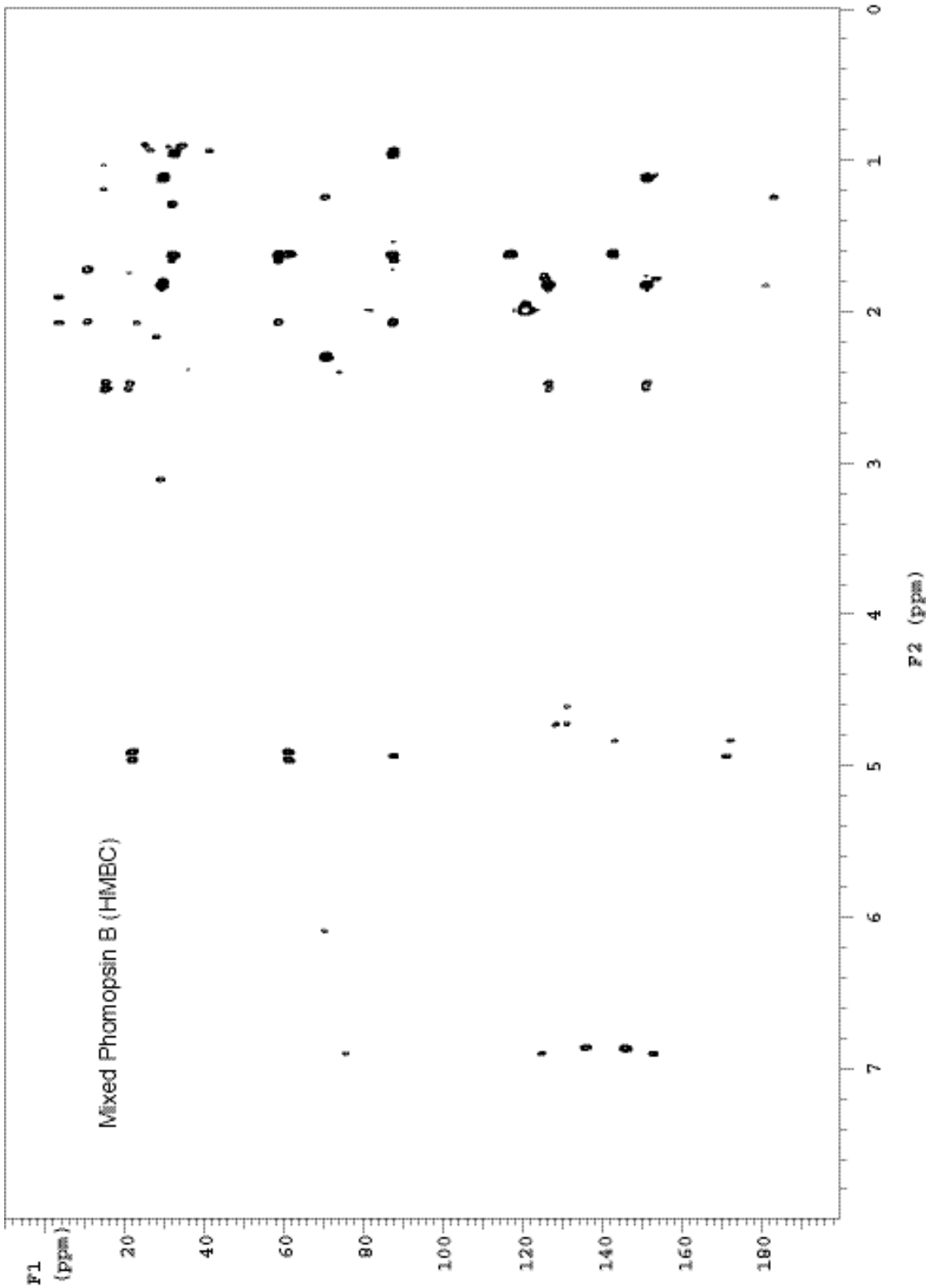

Natural Phomopsin B (HSQC)
F1 (ppm)
F2 (ppm)
0
1
2
3
4
5
6
7
20
40
60
80
100
120
140


Synthetic Phomopsin B (HSQC)
F1 (ppm)
F2 (ppm)
20
40
60
80
100
120
140
0
1
2
3
4
5
6
7


Mixed Phomopsin B (HSQC)
F1 (ppm)
F2 (ppm)
20
40
60
80
100
120
140
0
1
2
3
4
5
6
7


Natural Phomopsin B (HMBC)
F1 (ppm)
F2 (ppm)
20
40
60
80
100
120
140
160
180
0
1
2
3
4
5
6
7


Synthetic Phomopsin B (HMBC)
F1 (ppm)
F2 (ppm)
20
40
60
80
100
120
140
160
180
0
1
2
3
4
5
6
7


Mixed Phomopsin B (HMBC)
F1 (ppm)
F2 (ppm)
20
40
60
80
100
120
140
160
180
0
1
2
3
4
5
6
7

References

1 G. Ageno, L. Banfi, G. Cascio, G. Guanti, E. Manghisi, R. Riva, V. Rocca, *Tetrahedron* **1995**, *51*, 8121.

2 A. M. Sawayama, H. Takana, T. J. Wandless, *J. Org. Chem.* **2004**, *69*, 8810.

3 D. A. Evans, J. M. Janey, N. Magomedov, J. S. Tedrow, *Angew. Chem.* **2001**, *113*, 1936; *Angew. Chem. Int. Ed.*, **2001**, *40*, 8810.

4 R. E. Shute, D. H. Rich, *Synthesis*, **1987**, 346.

5 M. M. Stohlmeyer, H. Tanaka, T. J. Wandless, *J. Am. Chem. Soc.* **1999**, *121*, 6100.

6 T. F. Woiwode, T. J. Wandless, *J. Org. Chem.* **1999**, *64*, 7670.

7 J. R. Malpass, D. A. Hemmings, A. L. Wallis, S. R. Fletcher, S. Patel, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1044.