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Supporting Information

Synthesis of Chondramide A Analogues with Modified β-Tyrosine and Their Biological Evaluation

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Supporting Information

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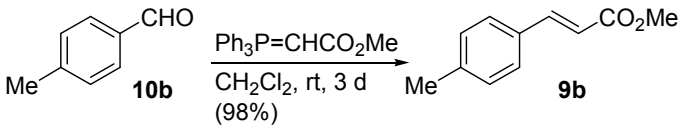
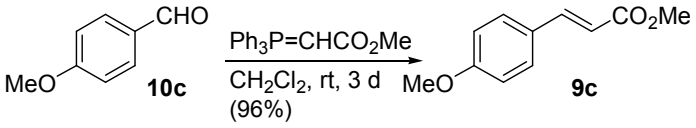
Experimental Section

General. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, dimethylformamide, methanol, ethyl acetate, benzene, and triethylamine were distilled from CaH_2. Distilled petroleum ether (petroleum ether) with a boiling range of 40–60 °C was used. Reactions were generally run under argon or nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used without purification. ^{1}H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm), MeOD (δH 3.30, δC 49.0 ppm), DMSO-d_6 (δH 2.49, δC 39.5 ppm). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization(ESI). Column chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography: Machery-Nagel Polygram Sil G/UV_{254}. Optical rotations: JASCO Polarimeter P-1020, sodium D line (589 nm), c = g × 100 mL^{-1}. From the depsipeptides **22** onwards, chondramide A numbering was used.

Procedures for Scheme 2



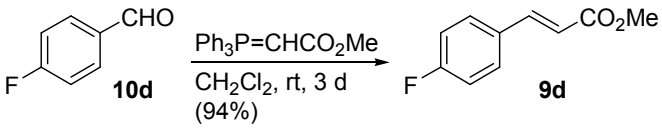
(*E*)-Methyl 3-*p*-tolylacrylate (9b). To a solution of 4-methylbenzaldehyde (**10b**) (2.00 g, 16.6 mmol) in CH_2Cl_2 (65 mL) was added methyl (triphenylphosphoranylidene)acetate (6.66 g, 19.9 mmol) in one portion. The mixture was stirred at room temperature for 3 d and then concentrated in vacuo. The residue containing Ph_3P=O and the acrylate was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give the cinnamate[1,2] **9b** (2.73 g, 96%) as a colorless solid, m.p. = 85 °C. R_f = 0.34 (petroleum ether/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.39 (d, J = 16.0 Hz, 1H, 2-H), 7.18 (d, J = 8.1 Hz, 2H, Ar), 7.41 (d, J = 8.1 Hz, 2H, Ar), 7.66 (d, J = 16.0 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (CH_3), 51.6 (OCH_3), 116.7 (C-2), 128.0 (Ar), 129.6 (Ar), 131.6 (Ar), 140.7 (Ar), 144.8 (C-3), 167.6 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{12}O_2$ [*M*+Na]$^+$: 199.07295; found: 199.072842.



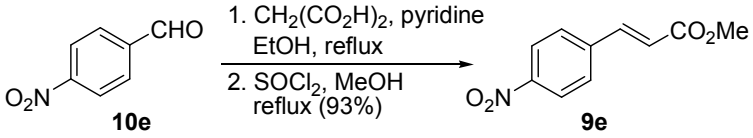
(*E*)-Methyl 3-(4-methoxyphenyl)acrylate (9c). To a solution of anisaldehyde **10c** (2.00 g, 14.7 mmol) in CH_2Cl_2 (60 mL) was added methyl (triphenylphosphoranylidene)acetate (5.90 g, 17.6 mmol) in one portion. The mixture was stirred at room temperature for 3 d and then concentrated in vacuo. The residue containing Ph_3P=O and the acrylate was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give the cinnamate[1] **9c** (2.73 g, 96%) as a colorless solid, m.p. = 86 °C. R_f = 0.38 (petroleum ether/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.30 (d, J = 16.0 Hz, 1H, 2-H), 6.89 (d, J = 8.9 Hz, 2H, Ar), 7.46 (d, J = 8.7 Hz, 2H, Ar), 7.64 (d, J = 15.8 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5 (OCH_3), 55.3

[1] M. Hatsuda, T. Kuroda, M. Seki, *Synth. Commun.* **2003**, *33*, 427-434.
[2] G. Moyna, H. J. Williams, A. I. Scott, *Synth. Commun.* **1996**, *26*, 2235-2239.

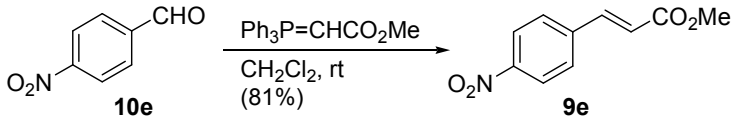
(OCH_3), 114.3 (Ar), 115.2 (C-2), 127.1 (Ar), 129.7 (Ar), 144.5 (C-3), 161.4 (CO), 167.7 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{12}O_3$ $[M+Na]^+$: 215.06787; found: 215.06788.



(*E*)-Methyl 3-(4-fluorophenyl)acrylate (9d). To a solution of 4-fluorobenzaldehyde (**10d**) (2.00 g, 16.1 mmol) in CH_2Cl_2 (65 mL) was added methyl (triphenylphosphoranylidene)acetate (6.45 g, 19.3 mmol) in one portion. The mixture was stirred at room temperature for 3 d and then concentrated in vacuo. The residue containing $Ph_3P=O$ and the acrylate was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give the cinnamate[2,3] **9d** (2.73 g, 94%) as a colorless solid, m.p. = 74 °C. R_f = 0.29 (petroleum ether/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OCH_3), 6.34 (d, *J* = 16.0 Hz, 1H, 2-H), 7.06 (dd, *J* = 8.7, 8.7 Hz, 2H, Ar), 7.49 (dd, *J* = 8.6 Hz, 2H, Ar), 7.64 (d, *J* = 16.0 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7 (OCH_3), 115.6 (d, *J* = 22.0 Hz, Ar), 117.5 (d, *J* = 2.2 Hz, C-2), 129.9 (d, *J* = 8.8 Hz, Ar), 130.6 (d, *J* = 3.7 Hz, Ar), 143.5 (C-3), 163.9 (d, *J* = 251.0 Hz, Ar), 167.3 (CO); HRMS (ESI): *m/z*: calcd for $C_{10}H_9FO_2$ $[M+Na]^+$: 203.04788; found: 203.04768.

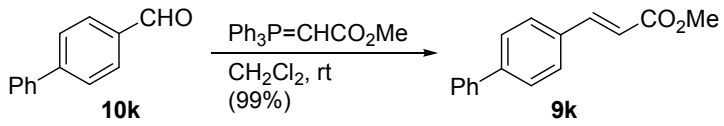


(*E*)-Methyl 4-nitrocinnamate (9e) (by Knoevenagel reaction). A solution of nitrobenzaldehyde (1.51 g, 0.01 mol), malonic acid (1.14 g, 1.1 equiv), and pyridine (0.25 mL, 0.31 equiv) in ethanol (2 mL) was heated at reflux. Already after 10–15 min a white solid began to precipitate. After 1.5 h, when TLC (EtOAc/petroleum ether, 1:2) indicated complete consumption of the aldehyde, the reaction mixture was cooled and acidified with diluted aqueous HCl. The precipitate was filtered, washed with water and dried in vacuo to afford crude but pure (2*E*)-3-(4-nitrophenyl)acrylic acid in quantitative yield (note: the free acid is soluble in acetone, DMSO, but hardly soluble in CH_2Cl_2, EtOAc). It was taken up in methanol (20 mL), thionyl chloride (1.3 equiv) was carefully added and the resulting suspension was heated at reflux for 1 h. At this time TLC (EtOAc/petroleum ether, 1:2) indicated complete consumption of the acid and the volume of precipitates visually increased. The product was obtained by crystallization directly from the reaction mixture as follows. The reaction mixture was concentrated in vacuo till a thick suspension resulted, that was filtered on a glass frit and the precipitate was washed with a small amount of cold methanol to afford 1.52 g (93%) of pure methyl (2*E*)-3-(4-nitrophenyl)acrylate (**9e**) as a slightly yellow solid. Analytical data are in agreement with literature data.[4]

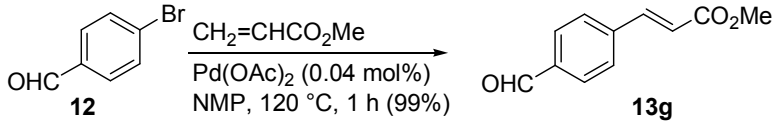


[3] (a) M. Beck, S. Jaunich, A. W. Frahm, *Arch. Pharm.* **1986**, *319*, 29-37; (b) G. Xie, P. Chellan, J. Mao, K. Chibale, G. S. Smith, *Adv. Synth. Catal.* **2010**, *352*, 1641-1647.
[4] Z. Zhang, Z. Wang, *J. Org. Chem.* **2006**, *71*, 7485-7487.

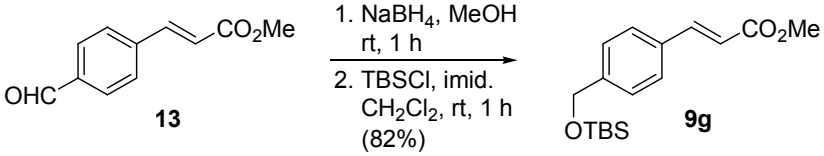
(*E*)-Methyl 4-nitrocinnamate (9e) (by Wittig reaction). Taking advantage of the low solubility of the product in cold methanol, the following one-step Wittig reaction procedure was efficiently applied. A solution of nitrobenzaldehyde (1.51 g, 0.01 mol), methyl (triphenylphosphoranylidene)acetate (4.0 g, 1.2 equiv) in CH_2Cl_2 (20 mL) was stirred overnight (slighty exothermic at the beginning) at room temperature. Then it was concentrated in vacuo to dryness, the residue was suspended in a small amount of methanol, enough to dissolve the bulk of triphenylphosphineoxide, the precipitate was filtered and washed with cold methanol to afford pure methyl (2*E*)-3-(4-nitrophenyl)acrylate (**9e**) (1.68 g, 81%).



(*E*)-Methyl 4-phenylcinnamate (9k). This was obtained by the same procedure as (2*E*)-3-(4-nitrophenyl)acrylate (**9e**). Thus, a solution of 4-biphenylcarbaldehyde (**10k**) (1.09 g, 6.0 mmol) and methyl (triphenylphosphoranylidene)acetate (2.40 g, 1.2 equiv) in CH_2Cl_2 (15 mL) was stirred at room temperature overnight. To monitor the progress of the reaction, a small sample was taken, evaporated and directly analyzed by NMR. (If the reaction was not finished completely, then additional methyl (triphenylphosphoranylidene)acetate should be added to achieve complete conversion.) The mixture was concentrated in vacuo to dryness, the residue was suspended in a small amount of methanol (but enough to dissolve the bulk of triphenylphosphineoxide), the precipitate was filtered and washed with cold methanol to afford pure methyl (2*E*)-methyl 4-phenylcinnamate (**9k**) (1.42 g, 99%). The analytical data were in agreement with previously reported data.[5]

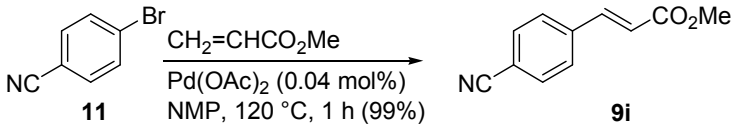


(*E*)-Methyl 4-formylcinnamate (13). A dry Schlenk vessel was charged with anhydrous NaOAc (2.7 g, 33.0 mmol), *p*-bromobenzaldehyde (5.55 g, 30.0 mmol), $Pd(OAc)_2$ (2.6 mg, 0.04% mol) and anhydrous NMP (40 mL). Nitrogen atmosphere was applied and methyl acrylate (3.9 mL, 43.3 mmol, 1.4 equiv) was introduced via syringe and the reaction mixture was heated at 115–120 °C for 40–60 min to complete the reaction (TLC control EtOAc/petroleum ether, 1:4, R_f 0.45). The resulting orange to red solution containing a white precipitate was diluted with water (100 mL) and extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed twice with water, once with saturated NaCl solution, dried over Na_2SO_4, and filtered. The solvent was evaporated in vacuo to leave crude methyl (2*E*)-3-(4-formylphenyl)acrylate (5.63 g, 99%) as a yellow solid, which was almost pure and was used in synthesis of cinnamate **9g** without further purification. The analytical data were in agreement with the previously reported ones.[6]

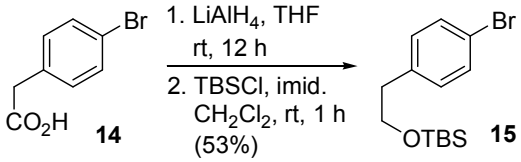


[5] R. Imashiro, M. Seki, *J. Org. Chem.* **2004**, *69*, 4216-4226.
[6] A. R. Hajipour, K. Karami, A. Pirisedigh, A. E. Ruoho, *J. Organomet. Chem.* **2009**, *694*, 2548-2554.

(*E*)-Methyl 4-[*tert*-butyldimethylsilyloxymethyl]cinnamate (9g). To a stirred solution of methyl (2*E*)-3-(4-formylphenyl)acrylate (**13**) (1.48 g, 7.8 mmol) in methanol (10 mL) was added $NaBH_4$ (0.3 g, 7.9 mmol) portionwise. The reaction mixture was stirred for 1 h at room temperature, and then it was concentrated, diluted with water and extracted with EtOAc. The organic phase was washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated to afford crude benzyl alcohol (1.42 g, quantitative yield, TLC: EtOAc/petroleum ether, 1:2, R_f 0.2). The alcohol was dissolved in dry CH_2Cl_2 (10 mL) and TBSCl (1.22 g, 8.1 mmol, 1.1 equiv) was added. Then, imidazole (0.554 g, 8.1 mmol, 1.1 equiv) was added portionwise while cooling the reaction flask in a cold water bath. The reaction mixture was stirred for 1 h at room temperature (TLC: EtOAc/petroleum ether, 1:2, R_f 0.8), the precipitate was filtered off and washed with portions of EtOAc. The filtrate was concentrated and the residue purified by flash chromatography (EtOAc/petroleum ether, 1:10) through a short column to afford the title compound (1.95 g, 82%) as an oil which crystallizes upon standing. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiCH_3$), 0.94 (s, 9H, $C(CH_3)_3$), 3.79 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2O), 6.41 (d, J = 16.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H, Ar), 7.48 (d, J = 8.1 Hz, 2H, Ar), 7.68 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 18.4 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 51.7 (OCH_3), 64.6 (CH_2Ar), 117.2, 126.4 (2C, Ar), 128.0 (2C, Ar), 133.0 (quat.), 144.1 (quat.), 144.8, 167.6 (CO_2CH_3).

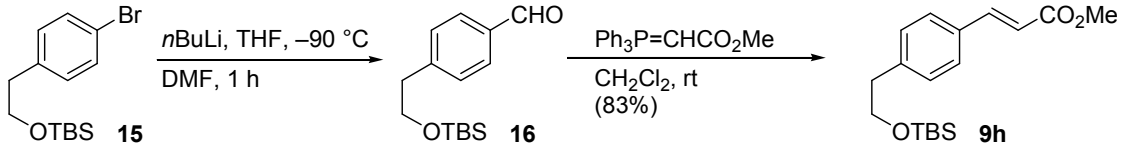


(*E*)-Methyl 3-(4-cyanophenyl)acrylate (9i). This compound was prepared from *p*-bromobenzonitrile by the same procedure as described for (2*E*)-3-(4-formylphenyl)acrylate in quantitative yield. Thus, a dry Schlenk vessel was charged with anhydrous NaOAc (0.9 g, 11 mmol), *p*-bromobenzonitrile (1.82 g, 10.0 mmol), $Pd(OAc)_2$ (1.0 mg, 0.04% mol) and anhydrous NMP (10 mL). Nitrogen atmosphere was applied and methyl acrylate (1.4 mL, 15.5 mmol, 1.55 equiv) was introduced via syringe and the reaction mixture was heated at 115–120 °C for 40–60 min to complete the reaction (TLC control: EtOAc/petroleum ether, 1:2, R_f 0.53). The resulting slightly orange solution containing a white precipitate was diluted with water (30 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed twice with water, once with saturated NaCl solution, dried over Na_2SO_4, and filtered. The solvent was evaporated in vacuo to leave crude acrylate **9i** (1.91 g, 100%) as a slightly yellow solid (TLC: EtOAc/petroleum ether, 1:2, R_f 0.53). Analytical data were in agreement with previously reported ones.[6]



1-Bromo-4-[(2-*tert*-butyldimethylsilyloxy)ethyl]benzene (15). To a solution of 2-(4-bromophenyl)acetic acid (**14**) (4.30 g, 20.0 mmol) in absolute THF (40 mL) was slowly added $LiAlH_4$ (0.608 g, 16.0 mmol, 0.8 equiv) while cooling the reaction flask in a cold water bath. The reaction mixture was stirred at room temperature overnight (actually, this may be too much), then water (2 mL) was carefully added, the resulting suspension was diluted with EtOAc, the precipitate was filtered off (using a paper filter) and washed three times with portions of EtOAc. The filtrate was concentrated and diluted with a small amount of CH_2Cl_2. This mixture was filtered and the filtrate concentrated in vacuo to leave the crude alcohol as slightly turbid oil (2.94 g, 73%). The crude alcohol was dissolved in CH_2Cl_2 (20 mL), TBSCl (2.31 g, 15.3 mmol, 1.05 equiv) was added

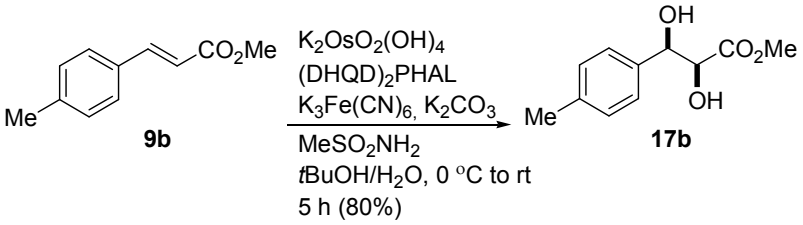
and imidazole (1.09 g, 16.0 mmol, 1.1 equiv) was added portionwise while cooling the reaction flask in a cold water bath. The reaction mixture was stirred for 1 h at room temperature (TLC control: EtOAc/petroleum ether, 1:2), the precipitate was filtered off, the filtrate was concentrated and the residue purified by flash chromatography (EtOAc/petroleum ether, 1:10) to afford silyl ether **15** (3.31 g, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.04 (s, 6H, $SiCH_3$), 0.85 (s, 9H, $C(CH_3)_3$), 2.75 (t, *J* = 6.8 Hz, 2H, $ArCH_2$), 3.79 (s, 3H, OCH_3), 3.76 (t, *J* = 6.8 Hz, 2H, CH_2O), 7.07 (d, *J* = 8.4 Hz, 2H, Ar), 7.38 (d, *J* = 8.4 Hz, 2H, Ar).



(*E*)-Methyl 3-(4-(2-(*tert*-butyldimethylsilyloxy)ethyl)phenyl)acrylate (9h). To a solution of aryl bromide **15** (2.629 g, 8.34 mmol) in absolute THF (35 mL) was added butyllithium (3.2 mL of a 2.5M solution in hexane, 1.05 equiv) dropwise at –90 °C followed by stirring of the mixture at –90–80 °C for 1 h. Then the reaction mixture was cooled to –100 °C and DMF (1.29 mL, 16.7 mmol, 2 equiv) was introduced quickly in one portion by syringe. The cooling bath was removed and the mixture was allowed to warm to –10 °C within 30 min and quenched with saturated aqueous NH_4Cl solution. Some EtOAc was added to the mixture to allow for better phase separation. The organic layer was washed with saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo to afford crude aldehyde **16** in essentially quantitative yield as colorless oil which was used in the next step without purification (the reaction was practically clean).

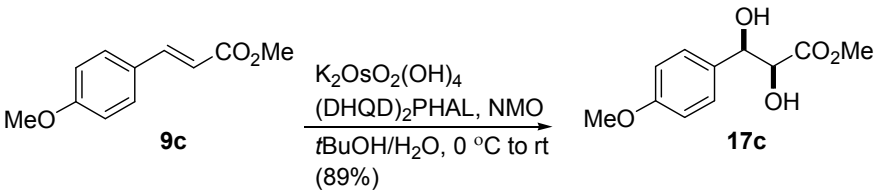
To the solution of crude aldehyde **16** in dry CH_2Cl_2 (20 mL) was added methyl (triphenylphosphoranylidene)acetate (3.0 g, 8.98 mmol) and the mixture was stirred overnight at room temperature. The reaction was conveniently controlled by NMR. The reaction mixture was concentrated in vacuo and the residue subjected to flash chromatography (petroleum ether/EtOAc, 4:1) to yield the cinnamic ester **9h** (2.01 g, 83% from bromide **15**) as a colorless oil. It should be noted, that complete conversion should be checked, otherwise it is much more difficult to separate cinnamate **9g** from the starting aldehyde **16** by chromatography. R_f (petroleum ether/EtOAc, 2:1) 0.75; ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.04 (s, 6H, $SiCH_3$), 0.85 (s, 9H, $C(CH_3)_3$), 2.82 (t, *J* = 6.9 Hz, 2H, $ArCH_2$), 3.79 (s, 3H, OCH_3), 3.80 (t, *J* = 6.9 Hz, 2H, CH_2O), 6.40 (d, *J* = 16.0 Hz, 1H, 2-H), 7.22 (d, *J* = 8.1 Hz, 2H, Ar), 7.43 (d, *J* = 8.1 Hz, 2H, Ar), 7.67 (d, *J* = 16.0 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($SiCH_3$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 39.4, 51.6 (OCH_3), 64.1 (CH_2Ar), 117.0 (=CH), 128.0 (C_{ar}), 129.8 (C_{ar}), 132.3 (C_{ar}), 142.1 (C_{ar}), 144.9 (=CH), 167.6 (CO_2CH_3).

Procedures for Scheme 3

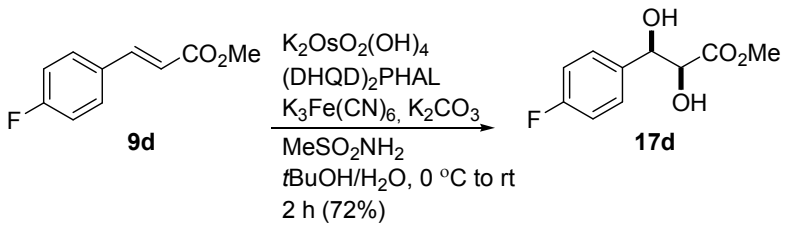


(2*S*,3*R*)-Methyl 2,3-dihydroxy-3-*p*-tolylpropanoate (17b). To a mixture of $K_3Fe(CN)_6$ (1.68 g, 5.11 mmol), $(DHQD)_2PHAL$ (13.0 mg, 0.017 mmol) and K_2CO_3 (0.71 g, 5.11 mmol) in *t*BuOH/H_2O (16 mL, 1:1) were added $K_2OsO_2(OH)_4$ (3.0 mg, 0.007 mmol) and $MeSO_2NH_2$ (0.162 g, 1.70 mmol). The mixture was stirred for 15 min, then cooled to 0 °C before cinnamate **9b** (0.30

g, 1.7 mmol) was added in one portion. The mixture was now stirred for 5 h while it warmed to room temperature. Thereafter, solid Na_2SO_3 (1.3 g), water (8 mL) and EtOAc (15 mL) were added. After separation of the layers, the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with cold 1N NaOH solution (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude diol was purified by flash chromatography (petroleum ether/EtOAc, 1:1) providing diol[7] **17b** (0.288 g, 80%) as a colorless solid, m.p. = 85 °C (ref.[7] m.p. 97.5–99 °C). R_f (petroleum ether/EtOAc, 3:2) 0.32; $[\alpha]^{20}_D$ = –8.2 (*c* 1.00, CH_2Cl_2) {ref.[7] *ent*-**17b** $[\alpha]^{25}_D$ = +6.3 (*c* 1.00, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 2.76 (d, *J* = 7.1 Hz, 1H, OH), 3.13 (d, *J* = 6.1 Hz, 1H, OH), 3.80 (s, 3H, OCH_3), 4.34 (dd, *J* = 6.1, 3.1 Hz, 1H, 2-H), 4.98 (dd, *J* = 7.1, 2.8 Hz, 1H, 3-H), 7.17 (d, *J* = 7.9 Hz, 2H, Ar), 7.27 (d, *J* = 8.1 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 52.8 (OCH_3), 74.3 (C-3), 74.1 (C-2), 126.1 (Ar), 129.1 (Ar), 136.1 (Ar), 137.8 (Ar), 173.2 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{14}O_4$ [*M*+Na]$^+$: 233.07843; found: 233.07837.



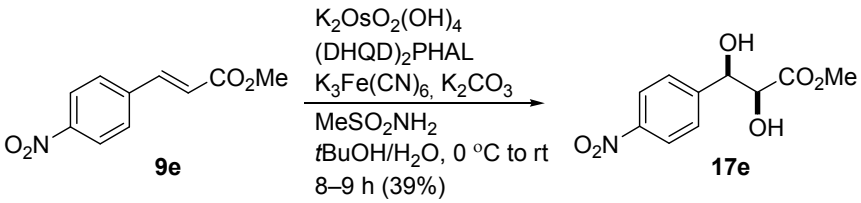
(2*S*,3*R*)-Methyl 2,3-dihydroxy-3-(4-methoxyphenyl)propanoate (17c). To a solution of cinnamate **9c** (1.00 g, 5.20 mmol) in *t*-BuOH (4 mL) were added successively $(DHQD)_2PHAL$ (18.0 mg, 0.026 mmol) and NMO (0.774 g, 5.57 mmol, 60% solution in H_2O, 1.24 mL). The mixture was cooled to 0 °C before $K_2OsO_2(OH)_4$ (4.0 mg, 0.01 mmol) was added. The cooling bath was removed and the mixture stirred for 2 h at room temperature. Then solid Na_2SO_3 (0.8 g), water (4 mL) and EtOAc (10 mL) were added. After separation of the layers, the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude diol was purified by flash chromatography (petroleum ether/EtOAc, 1:1) providing diol **17c** (1.05 g, 89%) as a colorless solid, m.p. = 103 °C (ref.[7] m.p. 106–107 °C). $[\alpha]^{20}_D$ = –5.8 (*c* 1.00, CH_2Cl_2) {ref.[7] *ent*-**17c** $[\alpha]^{25}_D$ = +5.5 (*c* 1.00, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (bs, 2H, 2 × OH), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.31 (d, *J* = 3.1 Hz, 1H, 2-H), 4.93 (d, *J* = 3.1 Hz, 1H, 3-H), 6.88 (d, *J* = 8.7 Hz, 2H, Ar), 7.31 (d, *J* = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 55.2 (OCH_3), 74.1 (C-3), 74.8 (C-2), 113.8 (Ar), 127.5 (Ar), 132.0 (Ar), 159.4 (Ar), 173.2 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{14}O_5$ [*M*+Na]$^+$: 249.07334; found: 249.07327.



(2*S*,3*R*)-Methyl 3-(4-fluorophenyl)-2,3-dihydroxypropanoate (17d). To a mixture of $K_3Fe(CN)_6$ (2.19 g, 6.66 mmol), $(DHQD)_2PHAL$ (17.0 mg, 0.022 mmol) and K_2CO_3 (0.92 g, 6.66 mmol) in *t*BuOH/H_2O (22 mL, 1:1) were added $K_2OsO_2(OH)_4$ (3.3 mg, 0.009 mmol) and $MeSO_2NH_2$ (0.211 g, 2.22 mmol). The mixture was stirred for 15 min, then cooled to 0 °C before cinnamate **9d** (0.40 g, 2.22 mmol) was added in one portion. The mixture was now stirred for 2 h while it warmed to

[7] P. Liu, W. He, Y. Zhao, P.-A. Wang, X.-L. Sun, X.-Y. Li, S.-Y. Zhang, *Chirality* **2008**, *20*, 75-83.

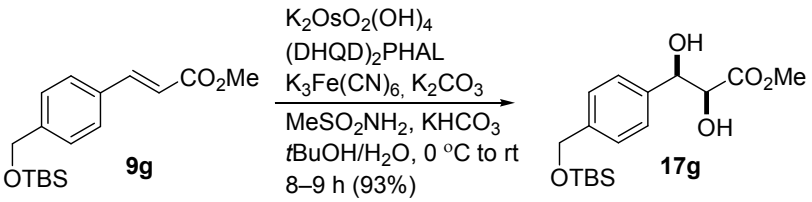
room temperature. Thereafter, solid Na_2SO_3 (1.7 g), water (10 mL) and EtOAc (20 mL) were added. After separation of the layers, the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with cold 1N NaOH solution (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude diol was purified by flash chromatography (petroleum ether/EtOAc, 1:1) providing diol **17d** (0.345 g, 72%) as a colorless solid, m.p. = 74 °C (ref.[7] m.p. 61.5–62.5 °C). R_f (petroleum ether/EtOAc, 3:2) 0.32; $[\alpha]^{20}_D$ = –8.6 (*c* 1.00, CH_2Cl_2) {ref.[7] *ent*-**17d** $[\alpha]^{25}_D$ = +9.1 (*c* 1.00, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (d, *J* = 6.9 Hz, 1H, OH), 3.27 (d, *J* = 6.1 Hz, 1H, OH), 3.78 (s, 3H, OCH_3), 4.30 (dd, *J* = 6.1, 3.1 Hz, 1H, 2-H), 4.96 (dd, *J* = 6.9, 3.1 Hz, 1H, 3-H), 7.00–7.07 (m, 2H, Ar), 7.33–7.38 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9 (OCH_3), 73.8 (C-3), 74.6 (C-2), 115.3 (d, *J* = 21.2 Hz, Ar), 128.0 (d, *J* = 8.1 Hz, Ar), 135.7 (d, *J* = 2.9 Hz, Ar), 162.5 (d, *J* = 246.6 Hz, Ar), 173.0 (CO); HRMS (ESI): *m/z* calcd for $C_{10}H_{11}FO_4$ $[M+Na]^+$: 237.05336; found: 237.05334.



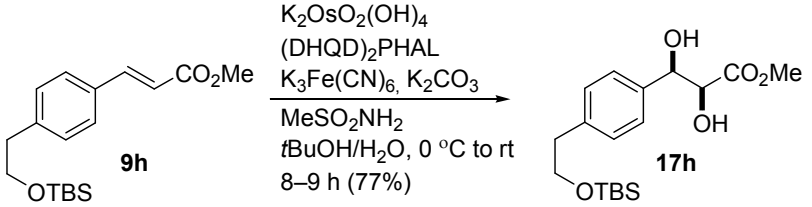
(2*S*,3*R*)-Methyl 3-(4-cyanophenyl)-2,3-dihydroxypropanoate (17e). A mixture of $K_3Fe(CN)_6$ (7.22 g, 22.0 mmol, 3 equiv), K_2CO_3 (3.04 g, 22.0 mmol, 3 equiv), $MeSO_2NH_2$ (0.70 g, 7.37 mmol, 1 equiv), $K_2OsO_2(OH)_4$ (10 mg, 0.027 mmol, 0.0037 equiv), and the ligand $(DHQD)_2PHAL$ (57 mg, 0.073 mmol, 0.01 equiv) was stirred in a mixture of water (35 mL) and *t*BuOH (35 mL) until dissolved and then the solution was cooled to 0 °C in an ice bath. At this point cinnamate **9e** (1.52 g, 7.34 mmol) was added and the reaction mixture was allowed to reach room temperature slowly while being stirred overnight, at which time a yellow suspension was formed and complete or almost complete conversion was observed according to TLC (petroleum ether/EtOAc, 1:1). Then solid Na_2SO_3 (9.2 g, 73.4 mmol, 10 equiv) was added and the mixture was stirred for several min. The suspension was filtered, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel, the organic phase was separated, and the water phase was extracted twice with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to afford pure diol **17e** (0.698 g, 39%) as a colorless solid.

Sometimes it was difficult to purify the diol from $CH_3SO_3NH_2$ (as a contaminant in different compounds comes at δ = 3.08–3.10 (s, 3H), 4.67–4.79 (bs, 2H)), but the sulfone amide impurity did not influence the next Mitsunobu azidation as was established later. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81 (bs, 1H, OH), 3.13 (bs, 1H, OH), 3.86 (s, 3H, OCH_3), 4.39 (bs, 1H, 2-H), 5.14 (bs, 1H, 3-H), 7.59 (d, *J* = 8.4 Hz, 2H, Ar), 8.23 (d, *J* = 8.4 Hz, 2H, Ar).

In one experiment, after extraction of the reaction mixture with THF/EtOAc, the organic extract was concentrated (but not till dyness) and some precipitate (the salt), insoluble in EtOAc, was isolated by filtration. It was taken up in diluted HCl and extracted with EtOAc. Upon evaporation of the solvent, white crystals were obtained, soluble in EtOAc, but insoluble in $CHCl_3$, that was proved to be an acid, the product of saponification of **17e**. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.16 (d, *J* = 2.8 Hz, 1H, 2-H), 5.04 (d, *J* = 2.8 Hz, 1H, 3-H), 7.65 (d, *J* = 8.6 Hz, 2H, Ar), 8.17 (d, *J* = 8.6 Hz, 2H, Ar).

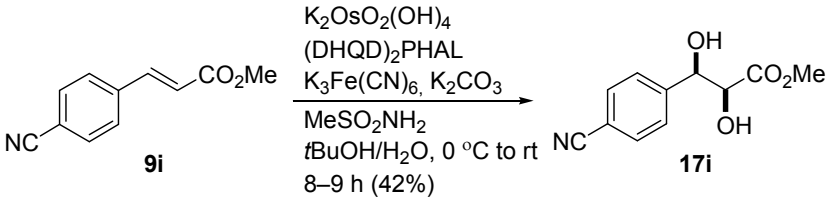


(2*S*,3*R*)-Methyl 3-(4-((*tert*-butyldimethylsilyloxy)methyl)phenyl)-2,3-dihydroxypropanoate (17g). Representative procedure. A mixture of $K_3Fe(CN)_6$ (3.68 g, 11.2 mmol, 3 equiv), K_2CO_3 (1.54 g, 11.2 mmol, 3 equiv), $KHCO_3$ (0.374 g, 3.74 mmol, 1 equiv), $MeSO_2NH_2$ (0.356 g, 3.74 mmol, 1 equiv), $K_2OsO_2(OH)_4$ (14 mg, 0.038 mmol, 0.01 equiv), and the ligand $(DHQD)_2PHAL$ (44 mg, 0.056 mmol, 0.015 equiv) was stirred in a mixture of water (18 mL) and *t*BuOH (18 mL) until dissolved and then the solution was cooled to 0 °C in an ice bath. At this point cinnamate **9g** (1.15 g, 3.74 mmol) was added and the reaction mixture was allowed to reach room temperature slowly while being stirred for 8–9 h, at which time a yellow suspension was formed and complete or almost complete conversion was observed according to TLC (petroleum ether/EtOAc, 1:1). Then solid Na_2SO_3 (1.74 g, 13.8 mmol, 3.7 equiv) was added and the mixture was stirred for several min. The suspension was filtered, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel, the organic phase was separated, and the water phase was extracted twice with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, gradient 2:1 → 1:1 → 0:1) to afford pure diol **17g** (1.18 g, 93%) as a colorless oil. $[\alpha]^{20}_D$ = –3.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.09 (s, 6H, $SiCH_3$), 0.93 (s, 9H, $C(CH_3)_3$), 2.68 (d, *J* = 7.1 Hz, 1H, OH), 3.06 (d, *J* = 6.1 Hz, 1H, OH), 3.81 (s, 3H, OCH_3), 4.36 (dd, *J* = 2.7, 6.1 Hz, 1H, 2-H), 4.73 (s, 2H, CH_2O), 5.00 (dd, *J* = 2.7, 6.4 Hz, 1H, 3-H), 7.32 (d, *J* = 8.4 Hz, 2H, Ar), 7.36 (d, *J* = 8.4 Hz, 2H, Ar); HMRS (ESI): *m/z*: calcd for $C_{17}H_{28}O_5Si$: 363.15982 $[M+Na]^+$; found: 363.15993.

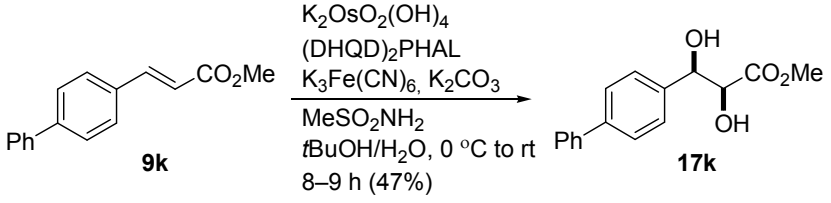


(2*S*,3*R*)-Methyl 3-(4-(2-(*tert*-butyldimethylsilyloxy)ethyl)phenyl)-2,3-dihydroxypropanoate (17g). A mixture of $K_3Fe(CN)_6$ (6.17 g, 18.8 mmol, 3.16 equiv), K_2CO_3 (2.60 g, 18.8 mmol, 3.16 equiv), $MeSO_2NH_2$ (0.596 g, 6.3 mmol, 1.1 equiv), $K_2OsO_2(OH)_4$ (9 mg, 0.024 mmol, 0.004 equiv), and the ligand $(DHQD)_2PHAL$ (49 mg, 0.063 mmol, 0.01 equiv) was stirred in a mixture of water (30 mL) and *t*BuOH (30 mL) until dissolved and then the solution was cooled to 0 °C in an ice bath. At this point cinnamate **9h** (1.90 g, 5.94 mmol) was added and the reaction mixture was allowed to reach room temperature slowly while being stirred overnight, at which time a yellow suspension was formed and complete or almost complete conversion was observed according to TLC (petroleum ether/EtOAc, 1:1). Then solid Na_2SO_3 (9.4 g, 74.6 mmol, 12.5 equiv) was added and the mixture was stirred for several minutes. The suspension was filtered, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel, the organic phase was separated, and the water phase was extracted twice with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, gradient 2:1 → 1:1) to afford pure diol **17h** (1.62 g, 77%) as a colorless oil. R_f (petroleum ether/EtOAc, 1:1) 0.53; $[\alpha]^{20}_D$ = –7.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02 (s, 6H, $SiCH_3$), 0.86 (s, 9H, $C(CH_3)_3$), 2.81 (t, *J* = 7.1 Hz, 2H, $ArCH_2$), 3.10 (brs, 1H, OH), 3.78 (t, *J* = 7.1 Hz, 2H, CH_2OTBS), 3.80 (s, 3H,

OCH_3), 4.34 (d, J = 2.8 Hz, 1H, 2-H), 4.99 (d, J = 2.8 Hz, 1H, 3-H), 7.20 (d, J = 8.4 Hz, 2H, Ar), 7.28 (d, J = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 39.2 ($ArCH_2$), 52.8 (OCH_3), 64.4 (CH_2O), 74.2, 74.7, 126.1 (2C, Ar), 129.3 (2C, Ar), 137.7 (C_{quat}), 139.1 (C_{quat}), 173.2 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{18}H_{30}O_5Si$: 377.17547 $[M+Na]^+$; found: 377.17549.



(2*S*,3*R*)-Methyl 3-(4-cyanophenyl)-2,3-dihydroxypropanoate (17i). A mixture of $K_3Fe(CN)_6$ (9.84 g, 30 mmol, 3 equiv), K_2CO_3 (4.14 g, 30 mmol, 3 equiv), $MeSO_2NH_2$ (0.95 g, 10 mmol, 1 equiv), $K_2OsO_2(OH)_4$ (15 mg, 0.04 mmol, 0.004 equiv), and the ligand $(DHQD)_2PHAL$ (78 mg, 0.1 mmol, 0.01 equiv) was stirred in a mixture of water (50 mL) and *t*BuOH (50 mL) until dissolved and then the solution was cooled to 0 °C in an ice bath. At this point cinnamate **9i** (1.87 g, 10.0 mmol) was added and the reaction mixture was allowed to reach room temperature slowly while being stirred overnight, at which time a yellow suspension was formed and complete or almost complete conversion was observed according to TLC (petroleum ether/EtOAc, 1:1). Then solid Na_2SO_3 (15 g, 119 mmol, 12 equiv) was added and the mixture was stirred for several min. The suspension was filtered, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel, the organic phase was separated, and the water phase was extracted twice with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, gradient 1:1 → 0:1) to afford pure diol **17i** (0.93 g, 42%) as a white solid. Analytical data are in agreement with previously reported.[8] With this diol it turned out to be more difficult to separate it from $CH_3SO_3NH_2$. The diol has limited solubility in EtOAc and CH_2Cl_2, but good solubility in acetone and methanol.



(2*S*,3*R*)-Methyl 3-(4-cyanophenyl)-2,3-dihydroxypropanoate (17k). A mixture of $K_3Fe(CN)_6$ (5.78 g, 17.6 mmol, 3.7 equiv), K_2CO_3 (2.03 g, 14.7 mmol, 3.1 equiv), $KHCO_3$ (1.18 g, 11.8 mmol, 2.5 equiv), $MeSO_2NH_2$ (0.167 g, 1.76 mmol, 0.37 equiv), $K_2OsO_2(OH)_4$ (6.5 mg, 0.0177 mmol, 0.0038 equiv), and the ligand $(DHQD)_2PHAL$ (22.9 mg, 0.0294 mmol, 0.0063 equiv) was stirred in a mixture of water (28 mL) and *t*BuOH (28 mL) until dissolved and then the solution was cooled to 0 °C in an ice bath. At this point cinnamate **9k** (1.12 g, 4.7 mmol) was added and the reaction mixture was allowed to reach room temperature slowly while being stirred overnight, but complete conversion was not reached. After work up as previously, a crude mixture (0.937 g), containing 49% w/w of unreacted cinnamate, 11% w/w $MeSO_2NH_2$ and **17k** was obtained, that was subjected to a second round of oxidation with $K_3Fe(CN)_6$ (1.90 g, 5.79 mmol, 3 equiv), K_2CO_3 (0.67 g, 4.9 mmol, 2.5 equiv), $KHCO_3$ (0.39 g, 3.9 mmol, 2 equiv), $K_2OsO_2(OH)_4$ (5.1 mg, 0.0139 mmol, 0.0072 equiv), and the ligand $(DHQD)_2PHAL$ (19 mg, 0.0244 mmol, 0.013 equiv) in water (10

[8] E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1996**, *118*, 319-329.

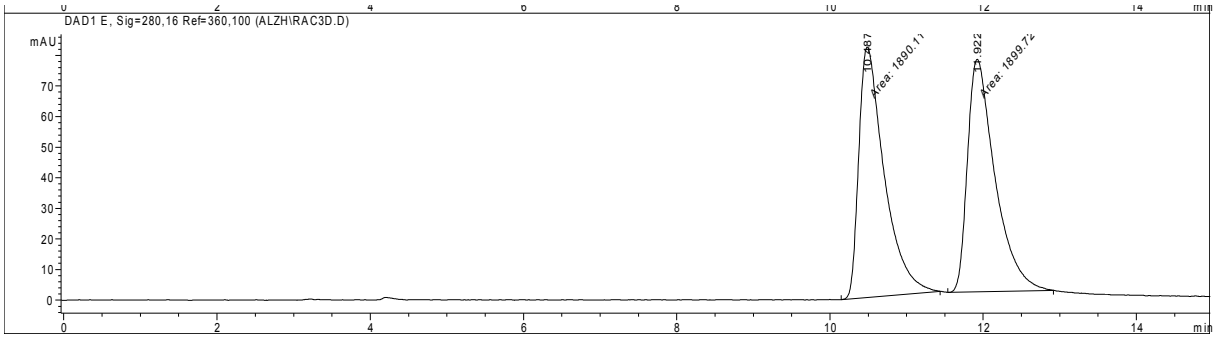
mL), *t*BuOH (10 mL) and CH_2Cl_2 (4 mL). This time, NMR of crude mixture indicated presence of 8% of starting cinnamate unreacted and at this point the reaction was stopped. After work up as previously, the residue was purified by flash chromatography (petroleum ether/EtOAc, gradient 2:1 → 1:1 → 0:1) to afford pure diol **17k** (0.267 g) and a solid mixture of **17k** with $MeSO_2NH_2$ (0.514 g, containing 90% w/w of **17k**). This mixed fraction was washed with diluted aqueous KOH and, subsequently, with water on a glas frit to afford pure **17k** (0.336 g) as a colorless solid, indicating also a mass loss due to concurrent ester saponification. Total yield was 0.603 g (47%). Diol **17k** has good solubility in CH_2Cl_2, but limited in EtOAc. R_f (EtOAc) 0.6; $[\alpha]^{20}_D = -8.8$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (d, *J* = 7.1 Hz, 1H, OH), 3.13 (d, *J* = 5.6 Hz, 1H, OH), 3.84 (s, 3H, OCH_3), 4.42 (dd, *J* = 2.5, 5.6 Hz, 1H, 2-H), 5.08 (app d, 1H, 3-H), 7.34 (t, *J* = 7.4 Hz, 1H, Ar), 7.42–7.49 (m, 5H, Ar), 7.57–7.61 (d+d, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.0 (OCH_3), 74.1, 74.6, 126.6 ($2C_{ar}$), 127.1 ($2C_{ar}$), 127.2 ($2C_{ar}$), 127.4 (C_{ar}), 128.8 ($2C_{ar}$), 138.9 (C_{ar}), 140.7 (C_{ar}), 141.0 (C_{ar}), 173.1 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{16}H_{16}O_4$: 295.09408 $[M+Na]^+$; found: 295.09407.

ee-Determination for some of the diols 17

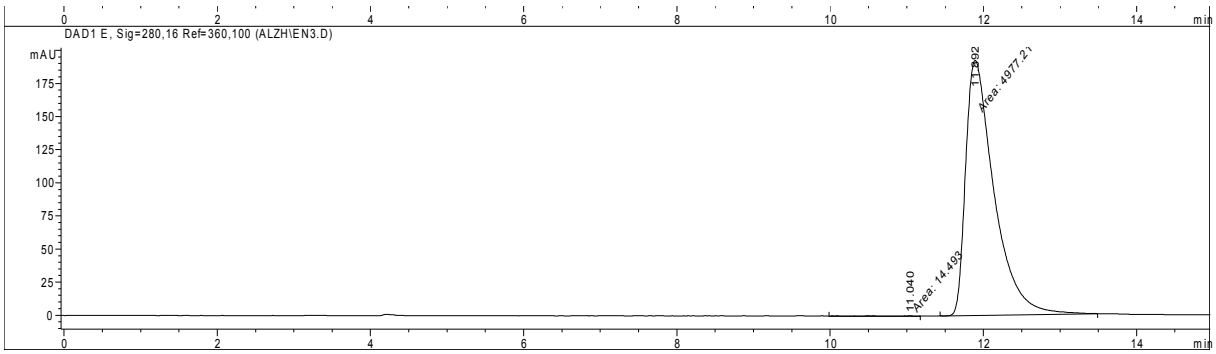
Column Chiralcel OJ-H

diol **17e**:

NO_2 rac, hexane/*i*PrOH 70:30, flow 1 mL min^{-1}, injection 5 μL

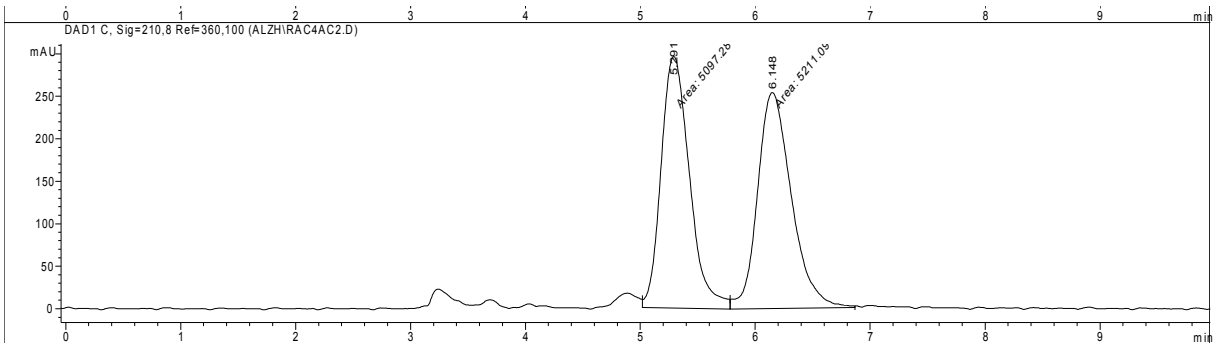


NO_2 enantiomer, hexane/*i*PrOH 70:30, flow 1 mL min^{-1}, injection 5 μL

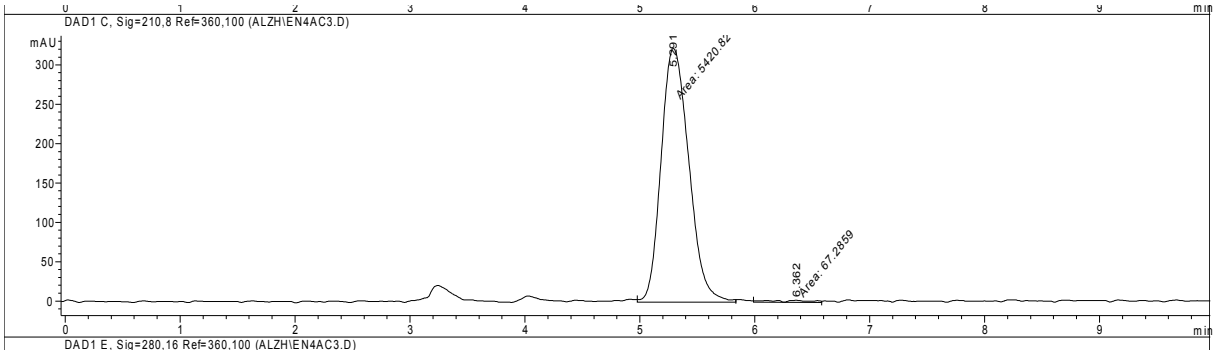


diol **17g**:

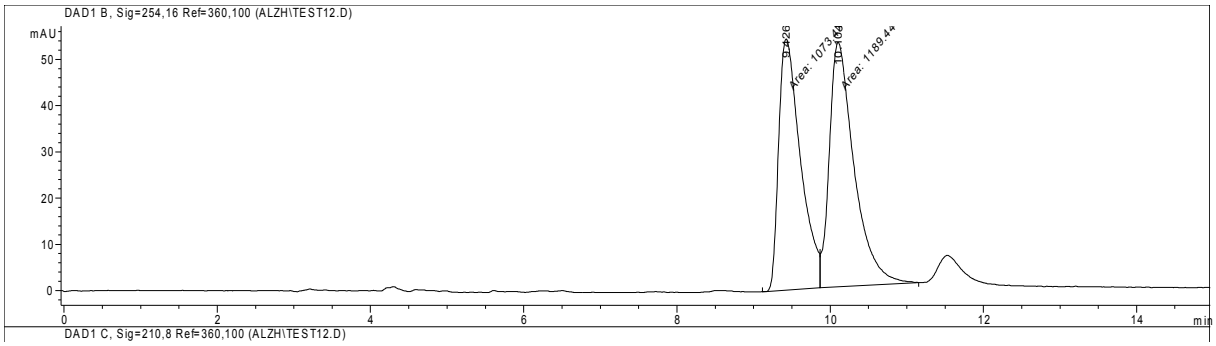
CH_2OTBS acetonide rac, hexane/*i*PrOH 95:5, flow 1 mL min^{-1}, injection 5 μL



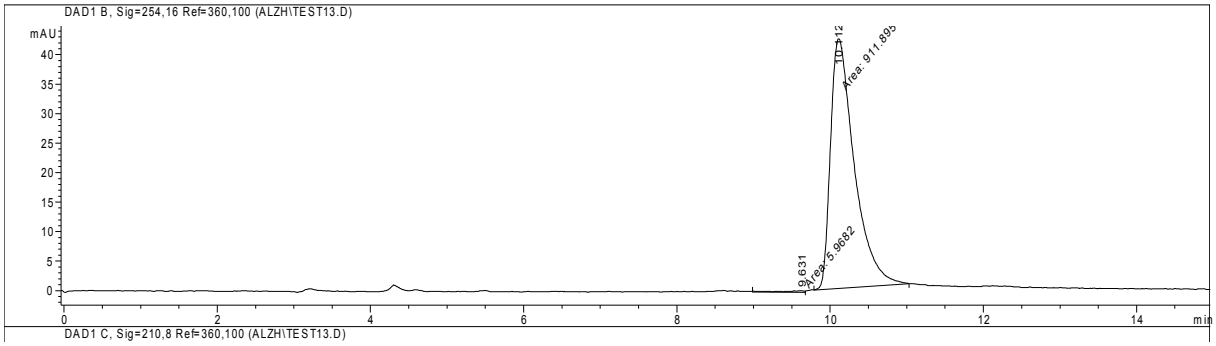
CH_2OTBS acetonide enantiomer, hexane/*i*PrOH 95:5, flow 1 mL min^{-1}, injection 5 μL



diol **17i**:
CN rac, hexane/*i*PrOH 70:30, flow 1 mL min^{-1}, injection 5 μL



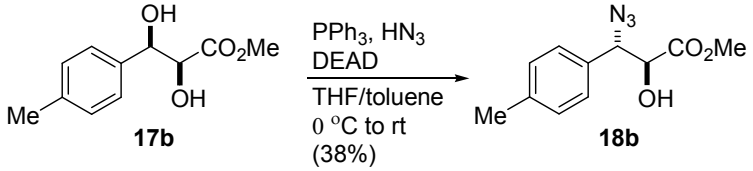
CN enantiomer, hexane/*i*PrOH 70:30, flow 1 mL min^{-1}, injection 5 μL



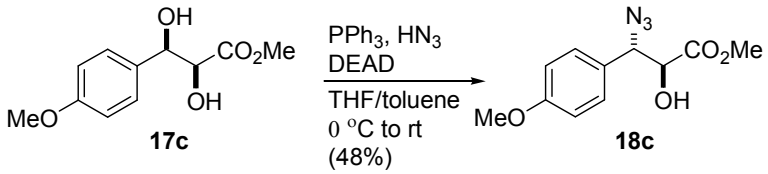
Ph diol **17k** did not provide good separation neither as a diol nor as acetonide.

Preparation of hydrazoic acid solution: **Caution**: Hydrazoic acid is a highly volatile, toxic and explosive liquid in individual state. However, in solution it is stable and safe. In this study solutions up to 5M were used. Sodium azide (3.0 g, 46 mmol) was mixed with water (1.5 mL) and toluene (10 mL). The suspension was cooled to near 0 °C and concentrated H_2SO_4 (~2 g, ~1.09 mL, 20 mmol) was carefully added while cooling and shaking the round bottom flask (stirring with magnetic stirring bar is not sufficient). Crystals were kneaded with a spatula shortly after the addition of the acid. Then the mixture was filtered under positive pressure and dried with Na_2SO_4 (there was no water phase remained, and no need to separate it from toluene solution). To rapidly estimate the resulting concentration of hydrazoic acid, a known amount of NaOH was dissolved in a small amount of water, phenolphthalein was added and the pink solution was titrated with the hydrazoic acid solution from an analytical pipette (the concentration was found to be 3.3M against theoretical 4.0M).

Note. In the following Mitsunobu reactions, the products **18e** and **18i** were slightly contaminated with diethyl hydrazodicarboxylate (~3 – 5 mol %), having signals δ = 1.28±0.01 (t, 6H), 4.22±0.01 (q, 4H). This impurity does not cause problems in the subsequent steps.

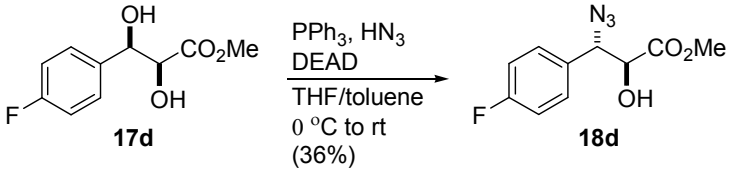


(2*S*,3*S*)-Methyl 3-azido-2-hydroxy-3-*p*-tolylpropanoate (18b). To a stirred solution of diol **17b** (0.500 g, 2.38 mmol), triphenylphosphine (0.749 g, 2.85 mmol, 1.2 equiv), hydrazoic acid (1.44 mL, 3.3M in toluene, 2.0 equiv) in THF (7.0 mL) at 0 °C was added DEAD (1.42 mL, 3.09 mmol, 40% wt. solution in toluene, 1.3 equiv) via syringe pump within 5 h. Then the cooling bath was removed and the resulting mixture was stirred for 18 h at ambient temperature. The mixture was treated with saturated $NaHCO_3$ solution (6 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to provide 3-azido propanoate **18b** (0.212 g, 38%) as a colorless oil. R_f (petroleum ether/EtOAc, 4:1) 0.25; $[\alpha]^{20}_D$ = +80.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 2.88 (d, *J* = 6.6 Hz, 1H, OH), 3.72 (s, 3H, OCH_3), 4.50 (dd, *J* = 6.7, 4.2 Hz, 1H, 2-H), 4.83 (d, *J* = 4.1 Hz, 1H, 3-H), 7.12–7.24 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (CH_3), 52.7 (OCH_3), 67.0 (C-3), 73.7 (C-2), 127.7 (C_{ar}), 129.4 (C_{ar}), 131.2 (C_{ar}), 138.8 (C_{ar}), 171.8 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{13}N_3O_3$ $[M+Na]^+$: 258.08491; found: 258.084882.

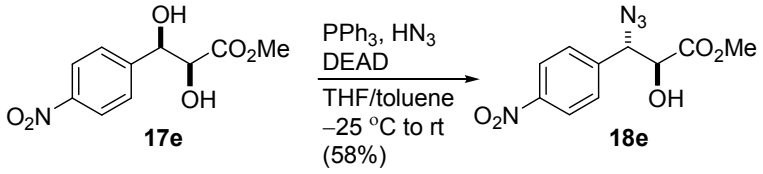


(2*S*,3*S*)-Methyl 3-azido-2-hydroxy-3-(4-methoxyphenyl)propanoate (18c). To a stirred solution of diol **17c** (0.40 g, 1.77 mmol), triphenylphosphine (0.557 g, 2.12 mmol, 1.2 equiv), hydrazoic acid (2.2 mL, 1.6M in toluene, 2.0 equiv) in THF (5.0 mL) at 0 °C was added DEAD (1.05 mL, 2.30 mmol, 40% wt. solution in toluene, 1.3 equiv) via syringe pump within 5 h. Then the cooling bath was removed and the resulting mixture was stirred for 18 h at ambient temperature. The mixture was treated with saturated $NaHCO_3$ solution (4 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography

(petroleum ether/EtOAc, 3:1) to provide 3-azido propanoate **18c** (0.211 g, 48%) as a colorless oil. A small amount of the *syn*-diastereomer (41 mg, 9%, R_f 0.25) was also isolated as an oil. R_f (petroleum ether/EtOAc, 3:1) 0.22; $[\alpha]^{20}_D$ = +92.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.89 (d, *J* = 6.6 Hz, 1H, OH), 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.50 (dd, *J* = 6.4, 4.1 Hz, 1H, 2-H), 4.81 (d, *J* = 4.1 Hz, 1H, 3-H), 6.89 (d, *J* = 8.7 Hz, 2H, Ar), 7.20–7.29 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 55.2 (OCH_3), 66.7 (C-3), 73.7 (C-2), 114.1 (C_{ar}),126.1 (C_{ar}), 129.1 (C_{ar}), 160.0 (C_{ar}), 171.8 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{13}N_3O_4$ [*M*+Na]$^+$: 274.07983; found: 274.079893.

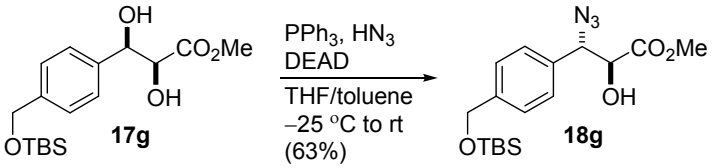


(2*S*,3*S*)-Methyl 3-azido-3-(4-fluorophenyl)-2-hydroxypropanoate (18d). To a stirred solution of diol **17d** (0.300 g, 1.40 mmol), triphenylphosphine (0.441 g, 1.68 mmol, 1.2 equiv), hydrazoic acid (0.85 mL, 3.3M in toluene, 2.0 equiv) in THF (4.0 mL) at 0 °C was added DEAD (0.835 mL, 1.82 mmol, 40% wt. solution in toluene, 1.3 equiv) via syringe pump within 5 h. Then the cooling bath was removed and the resulting mixture was stirred for 18 h at ambient temperature. The mixture was treated with saturated $NaHCO_3$ solution (4 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to provide 3-azido propanoate **18d** (0.119 g, 36%) as a colorless oil. R_f (petroleum ether/EtOAc, 4:1) 0.20; $[\alpha]^{20}_D$ = +41.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (bs, 1H, OH), 3.72 (s, 3H, OCH_3), 4.52 (d, *J* = 4.1 Hz, 1H, 2-H), 4.86 (d, *J* = 4.1 Hz, 1H, 3-H), 6.99–7.10 (m, 2H, Ar), 7.28–7.39 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 66.4 (C-3), 73.6 (C-2), 115.7 (d, *J* = 21.2 Hz, C_{ar}), 129.6 (d, *J* = 8.1 Hz, C_{ar}), 130.2 (d, *J* = 2.9 Hz, C_{ar}), 162.6 (d, *J* = 148.1 Hz, C_{ar}), 171.7 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{10}FN_3O_3$ [*M*+Na]$^+$: 262.05984; found: 262.05972.

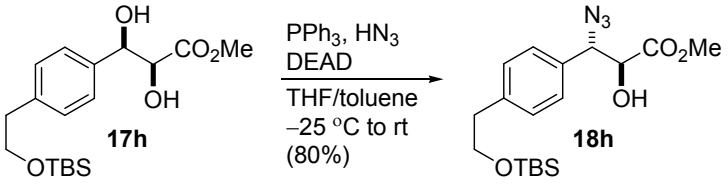


(2*S*,3*S*)-Methyl 3-azido-2-hydroxy-3-(4-nitrophenyl)propanoate (18e). To a stirred solution of diol **17e** (0.228 g, 0.946 mmol), triphenylphosphine (0.297 g, 1.14 mmol, 1.2 equiv), hydrazoic acid (0.86 mL, 3.3M in toluene, 3 equiv) in THF (2.0 mL) at –25 °C was added DEAD (0.56 mL, 0.535 g, 1.23 mmol, 40% wt. solution in toluene, 1.3 equiv), then the cooling bath was removed (slight evolution of N_2 was observed) and the resulting mixture was stirred overnight at ambient temperature (TLC control: petroleum ether/EtOAc, 1:1; NMR control: a sample portion was taken from the reaction mixture, evaporated and directly analyzed by NMR). Then the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 2:1) to yield 3-azido propanoate **18e** (0.145 g, 58%) as a slightly orange oil which solidified into a waxy solid upon standing. R_f (petroleum ether/EtOAc, 1:1) 0.55; $[\alpha]^{20}_D$ = +101.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11 (bs, 1H, OH), 3.73 (s, 3H, OCH_3), 4.58 (d, 1H, 2-H), 5.08 (d, *J* = 3.8 Hz, 1H, 3-H), 7.53 (d, *J* = 8.7 Hz, 2H, Ar), 8.23 (d, *J* = 8.7 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1 (OCH_3), 66.4 (C-3), 73.7 (C-2), 123.7 (C_{ar}), 128.7

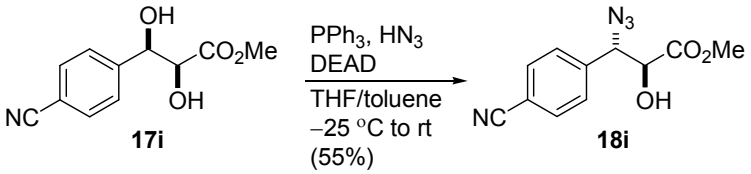
(C_{ar}), 141.8 (C_{ar}), 148.1 (C_{ar}), 171.3 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{10}H_{10}N_4O_5$ [*M*+Na]$^+$: 289.05434; found: 289.05431.



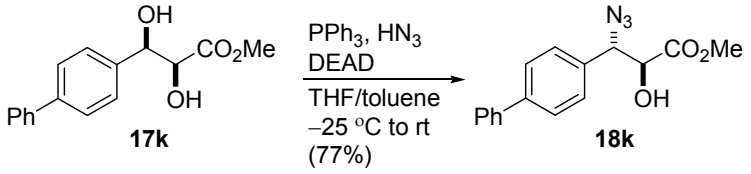
(2*S*,3*S*)-Methyl 3-azido-3-(4-((*tert*-butyldimethylsilyloxy)methyl)phenyl)-2-hydroxypropanoate (18g). To a stirred solution of diol **17g** (1.06 g, 3.1 mmol), triphenylphosphine (0.98 g, 3.72 mmol, 1.2 equiv), hydrazoic acid (4.7 mL, 2.0M in toluene, 3 equiv) in THF (7.0 mL) at –25 °C was added DEAD (1.7 mL, 4.03 mmol, 40% wt. solution in toluene, 1.3 equiv), then the cooling bath was removed (slight evolution of N_2 was observed) and the resulting mixture was stirred overnight at ambient temperature. Then the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:1 to 2:1) to yield 3-azido propanoate **18g** (0.719 g, 63%) as colorless oil. R_f (petroleum ether/EtOAc, 2:1) 0.6; $[\alpha]^{20}_D$ = +75.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiCH_3$), 0.93 (s, 9H, $C(CH_3)_3$), 2.88 (d, *J* = 6.6 Hz, 1H, OH), 3.71 (s, 3H, OCH_3), 4.51 (dd, *J* = 4.1, 6.6 Hz, 1H, 2-H), 4.73 (s, 2H, CH_2O), 4.86 (d, *J* = 4.1 Hz, 1H, 3-H), 7.29 (d, *J* = 8.4 Hz, 2H, Ar), 7.33 (d, *J* = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 18.4 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 52.7 (OCH_3), 64.5 (CH_2Ar), 67.0 (C-3), 73.7 (C-2), 126.2 (C_{ar}), 126.7 (C_{ar}), 132.7 (C_{ar}), 142.3 (C_{ar}), 171.8 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{17}H_{27}N_3O_4Si$ [*M*+Na]$^+$: 388.16630; found: 388.16639.



(2*S*,3*S*)-Methyl 3-azido-3-(4-(2-(*tert*-butyldimethylsilyloxy)ethyl)phenyl)-2-hydroxypropanoate (18h). To a stirred solution of diol **17h** (1.18 g, 3.33 mmol), triphenylphosphine (1.05 g, 4.00 mmol, 1.2 equiv), hydrazoic acid (4.2 mL, 2.4M in toluene, 3 equiv) in THF (7.0 mL) at –25 °C was added DEAD (1.83 mL, 4.33 mmol, 40% wt. solution in toluene, 1.3 equiv), then the cooling bath was removed (slight evolution of N_2 was observed) and the resulting mixture was stirred overnight at ambient temperature. Then the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:1 to 2:1) to yield 3-azido propanoate **18h** (0.997 g, 80%) as a colorless oil. R_f (petroleum ether/EtOAc, 2:1) 0.6; $[\alpha]^{20}_D$ = +70.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H, $SiCH_3$), 0.84 (s, 9H, $C(CH_3)_3$), 2.80 (t, *J* = 6.9 Hz, 2H, $ArCH_2$), 2.86 (brs, 1H, OH), 3.72 (s, 3H, OCH_3), 3.79 (t, *J* = 6.9 Hz, 2H, CH_2OTBS), 4.5 (d, *J* = 3.8 Hz, 1H, 2-H), 4.84 (d, *J* = 3.8 Hz, 1H, 3-H), 7.21 (d, *J* = 8.4 Hz, 2H, Ar), 7.24 (d, *J* = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($SiCH_3$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 39.2 ($ArCH_2$), 52.7 (OCH_3), 64.2 (CH_2O), 67.0 (C-3), 73.7 (C-2), 127.7 (C_{ar}), 129.6 (C_{ar}), 131.9 (C_{ar}), 140.3 (C_{ar}), 171.8 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{18}H_{29}N_3O_4Si$ [*M*+Na]$^+$: 402.18195; found: 402.18203.

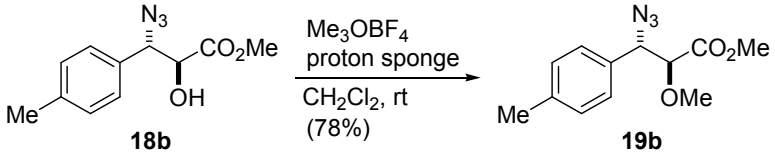


(2*S*,3*S*)-Methyl 3-azido-3-(4-cyanophenyl)-2-hydroxypropanoate (18i). To a stirred solution of diol **17i** (0.989 g of crude product containing 0.801 g of diol, 3.5 mmol), triphenylphosphine (1.10 g, 4.2 mmol, 1.2 equiv), hydrazoic acid (3.2 mL, 3.3M in toluene, 3 equiv) in THF (7.4 mL) at –25 °C was added DEAD (2.1 mL, 4.55 mmol, 40% wt. solution in toluene, 1.3 equiv), then the cooling bath was removed (slight evolution of N_2 was observed) and the resulting mixture was stirred overnight at ambient temperature. Then the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to yield 3-azido propanoate **18i** (0.472 g, 55%) as a colorless oil. R_f (petroleum ether/EtOAc, 2:1) 0.24; R_f (petroleum ether/EtOAc, 1:1) 0.68; $[\alpha]^{20}_D$ = +107.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14 (bs, 1H, OH), 3.71 (s, 3H, OCH_3), 4.55 (bs, 1H, 2-H), 4.94 (d, *J* = 3.8 Hz, 1H, 3-H), 7.46 (d, *J* = 8.3 Hz, 2H, Ar), 7.66 (d, *J* = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.0 (OCH_3), 66.6 (C-3), 73.7 (C-2), 112.7, 118.2, 128.4 (C_{ar}), 132.3 (C_{ar}), 139.9 (C_{ar}), 171.3 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{11}H_{10}N_4O_3$ [*M*+Na]$^+$: 269.06451; found: 269.06462.

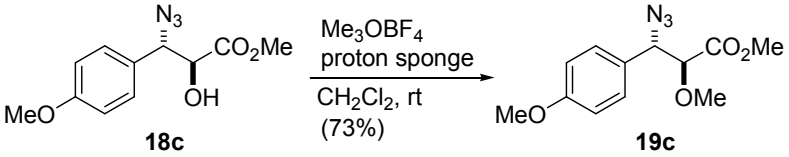


(2*S*,3*S*)-Methyl 3-azido-3-(biphenyl-4-yl)-2-hydroxypropanoate (18k). To a stirred solution of diol **17k** (0.514 g, 1.89 mmol), triphenylphosphine (0.594 g, 2.27 mmol, 1.2 equiv), hydrazoic acid (1.7 mL, 3.3M in toluene, 3 equiv) in THF (4.0 mL) at –25 °C was added DEAD (1.09 mL, 2.38 mmol, 40% wt. solution in toluene, 1.26 equiv), then the cooling bath was removed (slight evolution of N_2 was observed) and the resulting mixture was stirred overnight at ambient temperature. Then the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, petroleum ether/EtOAc 5:1 to 2.5:1) to yield 3-azido propanoate **18k** (0.433 g, 77%) as a colorless solid. R_f (petroleum ether/EtOAc, 2:1) 0.3–0.4; $[\alpha]^{20}_D$ = +121.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (bs, 1H, OH), 3.75 (s, 3H, OCH_3), 4.56 (d, *J* = 4.1 Hz, 1H, 2-H), 4.92 (d, *J* = 4.1 Hz, 1H, 3-H), 7.34–7.46 (m, 5H, Ar), 7.57–7.61 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 67.0 (C-3), 73.8 (C-2), 127.1 (C_{ar}), 127.3 (C_{ar}), 127.6 (C_{ar}), 128.2 (C_{ar}), 128.8 (C_{ar}), 133.3 (C_{ar}), 140.3 (C_{ar}), 141.7 (C_{ar}), 171.8 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{16}H_{15}N_3O_3$ [*M*+Na]$^+$: 320.10056; found: 320.10058.

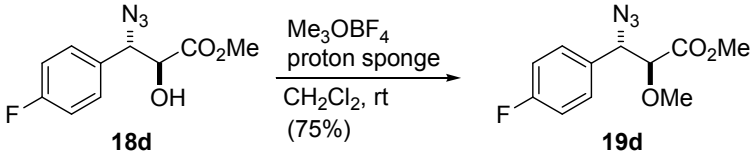
Note. In the following methylation reactions, if the substrate was contaminated with diethyl hydrazodicarboxylate, a product of methylation was formed, presumably a product of *N*-monomethylation, according to NMR. In the corresponding cases, this had the following signals δ = 1.31 (t, 6H), 3.20 (s, 3H), 4.25 (q, 4H). It causes no problems with the further steps.



(2*S*,3*S*)-Methyl 3-azido-2-methoxy-3-*p*-tolylpropanoate (19b). To a solution of α-hydroxy ester **18b** (0.260 g, 1.11 mmol) in dry CH_2Cl_2 (14 mL) was added trimethyloxonium tetrafluoroborate (0.572 g, 3.87 mmol, 3.5 equiv) and proton sponge (1.18 g, 5.53 mmol, 5 equiv). The flask was covered with aluminum foil. After stirring the suspension at ambient temperature for 20 h, the reaction mixture was treated with H_2O (10 mL), followed by separation of the layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 1N HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), saturated NaCl solution (10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 7:1) to yield methyl ether **19b** (0.215 g, 78%) as a colorless oil. R_f (petroleum ether/EtOAc, 7:1) 0.30; $[\alpha]^{20}_D$ = +47.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.98 (d, *J* = 6.6 Hz, 1H, 2-H), 4.72 (d, *J* = 6.9 Hz, 1H, 3-H), 7.18 (d, *J* = 7.9 Hz, 2H, Ar), 7.21–7.27 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (CH_3), 52.2 (OCH_3), 59.1 (OCH_3), 65.8 (C-3), 83.4 (C-2), 127.9 (C_{ar}), 129.4 (C_{ar}), 132.1 (C_{ar}), 138.7 (C_{ar}), 170.3 (CO); HRMS (ESI): *m/z*: calcd for $C_{12}H_{15}N_3O_3$ [*M*+Na]$^+$: 272.10056; found: 272.10062.

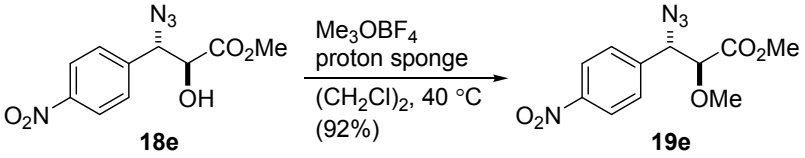


(2*S*,3*S*)-Methyl 3-azido-2-methoxy-3-(4-methoxyphenyl)propanoate (19c). To a solution of α-hydroxy ester **18c** (0.130 g, 0.517 mmol) in dry CH_2Cl_2 (4 mL) was added trimethyloxonium tetrafluoroborate (0.171 g, 1.16 mmol, 2.2 equiv) and proton sponge (0.354 g, 1.65 mmol, 3.2 equiv). The flask was covered with aluminum foil. After stirring the suspension at ambient temperature for 20 h, the reaction mixture was treated with H_2O (4 mL), followed by separation of the layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with 1N HCl (5 mL), saturated $NaHCO_3$ solution (5 mL), and saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 5:1) to yield methyl ether **19c** (0.100 g, 73%) as a colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.23; $[\alpha]^{20}_D$ = +56.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.35 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.97 (d, *J* = 6.4 Hz, 1H, 2-H), 4.70 (d, *J* = 6.6 Hz, 1H, 3-H), 6.89 (d, *J* = 8.9 Hz, 2H, Ar), 7.29 (d, *J* = 8.7 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.2 (OCH_3), 55.2 (OCH_3), 59.1 (OCH_3), 65.4 (C-3), 83.4 (C-2), 114.0 (C_{ar}), 127.1 (C_{ar}), 129.3 (C_{ar}), 159.9 (C_{ar}), 170.2 (CO); HRMS (ESI): *m/z*: calcd for $C_{12}H_{15}N_3O_4$ [*M*+Na]$^+$: 288.09548; found: 288.09558.

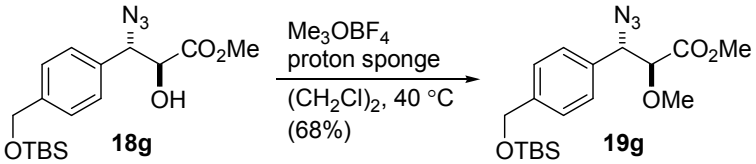


(2*S*,3*S*)-Methyl 3-azido-3-(4-fluorophenyl)-2-methoxypropanoate (19d). To a solution of α-hydroxy ester **18d** (0.084 g, 0.351 mmol) in dry CH_2Cl_2 (5 mL) was added trimethyloxonium tetrafluoroborate (0.182 g, 1.23 mmol, 3.5 equiv) and proton sponge (0.376 g, 1.76 mmol, 5 equiv). The flask was covered with aluminum foil. After stirring the suspension at ambient temperature for 20 h, the reaction mixture was treated with H_2O (4 mL), followed by separation of the layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with 1N HCl (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with

Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 6:1) to yield methyl ether **19d** (0.067 g, 75%) as a colorless oil. R_f (petroleum ether/EtOAc, 7:1) 0.22; $[\alpha]^{20}_D$ = +19.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.96 (d, *J* = 6.6 Hz, 1H, 2-H), 4.75 (d, *J* = 6.4 Hz, 1H, 3-H), 6.99–7.11 (m, 2H, Ar), 7.30–7.40 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3 (OCH_3), 59.2 (OCH_3), 65.2 (C-3), 83.3 (C-2), 115.7 (d, *J* = 22.0 Hz, C_{ar}), 129.9 (d, *J* = 8.8 Hz, C_{ar}), 131.0 (d, *J* = 2.8, C_{ar}), 162.9 (d, *J* = 248.1 Hz, C_{ar}), 170.0 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{12}FN_3O_3$ [*M*+Na]+: 276.07549; found: 276.07523.

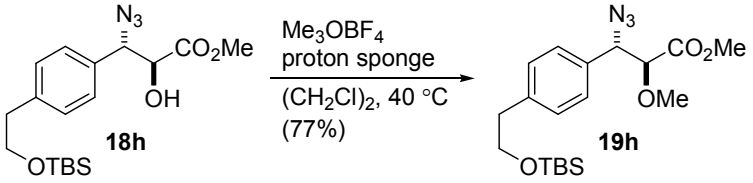


(2*S*,3*S*)-Methyl 3-azido-2-methoxy-3-(4-nitrophenyl)propanoate (19e). To a solution of α-hydroxy ester **18e** (0.495 g, 1.86 mmol) in dry 1,2-dichloroethane (1.9 mL) was added trimethyloxonium tetrafluoroborate (0.495 g, 3.35 mmol, 1.8 equiv) and proton sponge (0.876 g, 4.09 mmol, 2.2 equiv). The flask was covered with aluminum foil. After stirring the suspension at 40 °C overnight, a small probe was taken from the reaction mixture and quenched with $EtOAc/HCl_{aq}$ for TLC (petroleum ether/EtOAc, 1:1), that indicated full conversion. The reaction mixture was cooled, treated with $EtOAc/H_2O$, and acidified with 1N HCl to pH 2–3. The precipitate was filtered off and the filtrate was separated. The aqueous phase was extracted once with EtOAc and the combined organic extracts were washed with water, and saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 3:1 to 2:1) to yield methyl ether **19e** (0.48 g, 92%) as a slightly orange oil. R_f (petroleum ether/EtOAc, 2:1) 0.54; $[\alpha]^{20}_D$ = +49.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 3.99 (d, *J* = 6.1 Hz, 1H, 2-H), 4.89 (d, *J* = 6.1 Hz, 1H, 3-H), 7.55 (d, *J* = 8.7 Hz, 2H, Ar), 8.22 (d, *J* = 8.7 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 59.3 (OCH_3), 65.0 (C-3), 83.0 (C-2), 123.8 (C_{ar}), 129.0 (C_{ar}), 142.4 (C_{ar}), 148.1 (C_{ar}), 169.6 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{11}H_{12}N_4O_5$ $[M+Na]^+$: 303.06999; found: 303.07002.

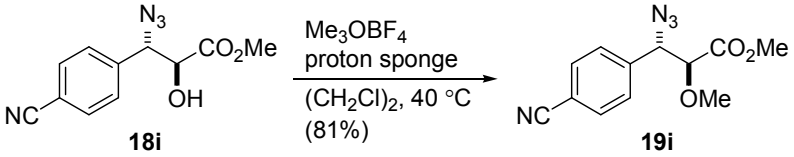


(2*S*,3*S*)-Methyl 3-azido-3-(4-((*tert*-butyldimethylsilyloxy)methyl)phenyl)-2-methoxypropanoate (19g). To a solution of α-hydroxy ester **18g** (0.674 g, 1.84 mmol) in dry 1,2-dichloroethane (3 mL) was added trimethyloxonium tetrafluoroborate (0.463 g, 3.13 mmol, 1.7 equiv) and proton sponge (0.803 g, 3.75 mmol, 2.04 equiv). The flask was covered with aluminum foil. After stirring the suspension at 40 °C overnight, the reaction mixture was cooled, treated with $EtOAc/H_2O$, and acidified with 1N HCl to pH 2–3. The precipitate was filtered off and the filtrate was separated. The aqueous phase was extracted once with EtOAc and the combined organic extracts were washed with water, and saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 10:1) to yield methyl ether **19g** (0.475 g, 68%) as a colorless oil. R_f (petroleum ether/EtOAc, 4:1) 0.49; $[\alpha]^{20}_D$ = +53.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiCH_3$), 0.93 (s, 9H, $C(CH_3)_3$), 3.34 (s, 3H, OCH_3), 3.74 (s, 3H, CO_2CH_3), 3.97 (d, *J* = 6.6, 1H, 2-H), 4.74 (s, 2H, CH_2O), 4.74 (d, *J* = 6.6 Hz, 1H, 3-H), 7.33 (s, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 18.4 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 52.2

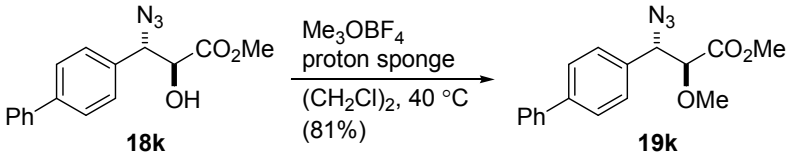
(OCH_3), 59.1 (OCH_3), 64.5 (CH_2Ar), 65.8 (C-3), 83.9 (C-2), 126.2 (C_{ar}), 127.9 (C_{ar}), 133.7 (C_{ar}), 142.2 (C_{ar}), 170.2 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{18}H_{29}N_3O_4Si$ $[M+Na]^+$: 402.18195; found: 402.18197.



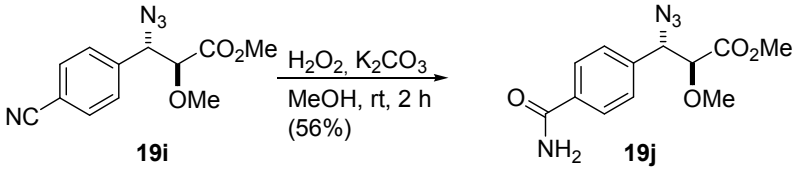
(2*S*,3*S*)-Methyl 3-azido-3-(4-(2-(*tert*-butyldimethylsilyloxy)ethyl)phenyl)-2-methoxypropanoate (19h). To a solution of α-hydroxy ester **18h** (0.897 g, 2.3 mmol) in dry 1,2-dichloroethane (3 mL) was added trimethyloxonium tetrafluoroborate (0.578 g, 3.91 mmol, 1.7 equiv) and proton sponge (0.886 g, 4.14 mmol, 1.8 equiv). The flask was covered with aluminum foil. After stirring the suspension at 40 °C overnight, the reaction mixture was cooled, treated with EtOAc/H_2O, and acidified with 1N HCl to pH 2–3. The precipitate was filtered off and the filtrate was separated. The aqueous phase was extracted once with EtOAc and the combined organic extracts were washed with water, and saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 10:1) to yield methyl ether **19h** (0.584 g, 77%, based on consumed material) as a colorless oil. The amount of recovered starting material was 0.167 g. R_f (petroleum ether/EtOAc, 4:1) 0.49; $[\alpha]^{20}_D$ = +56.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.06 (s, 6H, $SiCH_3$), 0.84 (s, 9H, $C(CH_3)_3$), 2.81 (t, *J* = 6.9 Hz, 2H, $ArCH_2$), 3.34 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.79 (t, *J* = 6.9 Hz, 2H, CH_2OTBS), 3.96 (d, *J* = 6.7 Hz, 1H, 2-H), 4.71 (d, *J* = 6.7 Hz, 1H, 3-H), 7.21 (d, *J* = 8.1 Hz, 2H, Ar), 7.27 (d, *J* = 8.1 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($SiCH_3$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 39.2 ($ArCH_2$), 52.2 (OCH_3), 59.1 (OCH_3), 64.2 (CH_2O), 65.7 (C-3), 83.4 (C-2), 127.9 (C_{ar}), 129.5 (C_{ar}), 132.9 (C_{ar}), 140.1 (C_{ar}), 170.3 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{19}H_{31}N_3O_4Si$ $[M+Na]^+$: 416.19760; found: 416.19771.



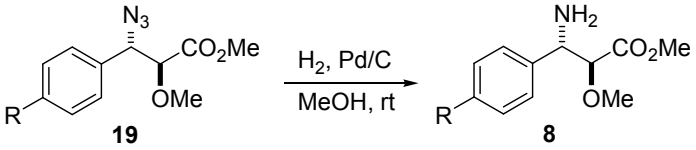
(2*S*,3*S*)-Methyl 3-azido-3-(biphenyl-4-yl)-2-methoxypropanoate (19i). To a solution of α-hydroxy ester **18i** (0.574 g, 2.3 mmol) in dry 1,2-dichloroethane (2.3 mL) was added trimethyloxonium tetrafluoroborate (0.621 g, 4.14 mmol, 1.8 equiv) and proton sponge (1.08 g, 5.06 mmol, 2.2 equiv). The flask was covered with aluminum foil. After stirring the suspension at 40 °C overnight, a small probe was taken from the reaction mixture and quenched with EtOAc/HCl_{aq} for TLC (petroleum ether/EtOAc, 1:1), that indicated full conversion. The reaction mixture was cooled, treated with EtOAc/H_2O, and acidified with 1N HCl to pH 2–3. The precipitate was filtered off and the filtrate was separated. The aqueous phase was extracted once with EtOAc and the combined organic extracts were washed with water, and saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 3:1 to 2:1) to yield methyl ether **19i** (0.489 g, 81%) as a colorless oil. R_f (petroleum ether/EtOAc, 2:1) 0.41; $[\alpha]^{20}_D$ = +59.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3H, OCH_3), 3.74 (s, 3H, CO_2CH_3), 3.97 (d, *J* = 6.3 Hz, 1H, 2-H), 4.82 (d, *J* = 6.3 Hz, 1H, 3-H), 7.48 (d, *J* = 8.3 Hz, 2H, Ar), 7.66 (d, *J* = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 59.2 (OCH_3), 65.3 (C-3), 82.9 (C-2), 112.7, 118.3, 128.8 (C_{ar}), 132.3 (C_{ar}), 140.5 (C_{ar}), 169.6 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{12}H_{12}N_4O_3$ $[M+Na]^+$: 283.08016; found: 283.08007.



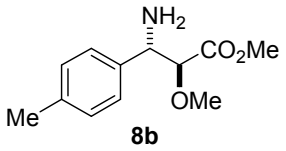
(2*S*,3*S*)-Methyl 3-azido-3-(biphenyl-4-yl)-2-methoxypropanoate (19k). To a solution of α-hydroxy ester **18k** (0.39 g, 1.31 mmol) in dry 1,2-dichloroethane (1.4 mL) was added trimethyloxonium tetrafluoroborate (0.349 g, 2.36 mmol, 1.8 equiv) and proton sponge (0.616 g, 2.2 equiv). The flask was covered with aluminum foil. After stirring the suspension at 40 °C overnight, a small probe was taken from the reaction mixture and quenched with EtOAc/HCl_{aq} for TLC (petroleum ether/EtOAc, 1:1), that indicated full conversion. The reaction mixture was cooled, treated with EtOAc/H_2O, and acidified with 1N HCl to pH 2–3. The precipitate was filtered off and the filtrate was separated. The aqueous phase was extracted once with EtOAc and the combined organic extracts were washed with water, and saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed (petroleum ether/EtOAc, 5:1 to 2:1) to yield methyl ether **19k** (0.329 g, 81%) as a colorless oil. R_f (petroleum ether/EtOAc, 2:1) 0.58; $[\alpha]^{20}_D$ = +86.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.39 (s, 3H, OCH_3), 3.77 (s, 3H, CO_2CH_3), 4.04 (d, *J* = 6.6 Hz, 1H, 2-H), 4.82 (d, *J* = 6.6 Hz, 1H, 3-H), 7.33–7.37 (m, 1H, Ar), 7.42–7.46 (m, 4H, Ar), 7.58–7.62 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3 (OCH_3), 59.2 (OCH_3), 65.7 (C-3), 83.4 (C-2), 127.1 (C_{ar}), 127.4 (C_{ar}), 127.5 (C_{ar}), 128.4 (C_{ar}), 128.8 (C_{ar}), 134.1 (C_{ar}), 140.4 (C_{ar}), 141.7 (C_{ar}), 170.2 (CO_2CH_3).



(2*S*,3*S*)-Methyl 3-azido-3-(4-carbamoylphenyl)-2-methoxypropanoate (19j). To a suspension of nitrile **19i** (65 mg, 0.25 mmol) and K_2CO_3 (30 mg) in methanol (0.53 mL) was added hydrogen peroxide (0.11 mL of 30% solution in water). The reaction mixture was stirred for 2 h at room temperature (TLC control: EtOAc). Then it was diluted with water and extracted twice with EtOAc. The combined organic extracts was washed with water, dried with Na_2SO_4, filtered, and evaporated. The residue was subjected to flash chromatography (EtOAc/petroleum ether, 1:1 to 1:0) to afford the amide **19j** (36 mg, 56%) as a colorless oil. A similar yield was obtained in DMF overnight. In contrast, in DMSO the reaction proceeded in several minutes and possibly could deliver higher yield, but in this case the product was not separable from the dimethyl sulfone by-product. R_f (EtOAc) 0.4; $[\alpha]^{20}_D$ = +60.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.35 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.99 (d, *J* = 6.4 Hz, 1H, 2-H), 4.81 (d, *J* = 6.4 Hz, 1H, 3-H), 6.29 (bs, 2H, NH_2), 7.43 (d, *J* = 8.3 Hz, 2H, Ar), 7.81 (d, *J* = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3 (OCH_3), 59.1 (OCH_3), 65.4 (C-3), 83.1 (C-2), 127.7 (C_{ar}), 128.3 (C_{ar}), 133.8 (C_{ar}), 139.1 (C_{ar}), 169.0, 169.9.

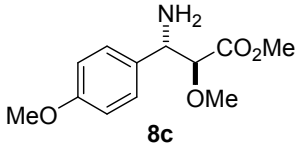


Catalytic hydrogenation of the azides 19 to the amino esters 8. Solutions of azides **19b** (Me), **19c** (OMe), **19d** (F), **19h** ($(CH_2)_2OTBS$), **19j** ($CONH_2$), and **19k** (Ph) (0.1–0.2M) in methanol were hydrogenated overnight in a round bottom flask connected to a hydrogen filled balloon, using 10% Pd on carbon (catalyst loading: 0.5–1 mol% Pd). Azides **19i** (CN) and **19g** (CH_2OTBS) were hydrogenated in shorter times, 4 and 2 h, respectively, to avoid reduction of the CN or benzylic C–O bond. In each case full conversion of the azides was observed. The solutions were filtered through celite and the filtrate evaporated to afford pure amino esters **8** in essentially quantitative yields. The amines **8** were used for the subsequent peptide coupling without further purification. When the hydrogenation of azide **19g** (CH_2OTBS) was performed overnight, formation of 20% of the corresponding methyl substituted derivative was observed.



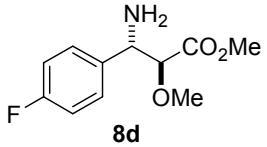
8b

(2*S*,3*S*)-Methyl 3-amino-2-methoxy-3-*p*-tolylpropanoate (8b). A solution of azide **19b** (0.197 g, 0.790 mmol) in MeOH (7 mL) was hydrogenated at room temperature for 5 h to provide 0.175 g (99%) of amine **8b** as a colorless oil. R_f (petroleum ether/EtOAc, 3:7) 0.23; $[\alpha]^{20}_D$ = –4.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (bs, 2H, NH_2), 2.31 (CH_3), 3.37 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.97 (d, *J* = 5.6 Hz, 1H, 2-H), 4.23 (d, *J* = 5.6 Hz, 1H, 3-H), 7.11 (d, *J* = 8.9 Hz, 2H, Ar), 7.18 (d, *J* = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 51.7 (OCH_3), 57.4 (C-3), 59.0 (OCH_3), 85.4 (C-2), 126.8 (C_{ar}), 129.0 (C_{ar}), 133.2 (C_{ar}), 138.5 (C_{ar}), 171.3 (CO); HRMS (ESI): *m/z*: calcd for $C_{12}H_{17}NO_3$ [*M*+Na]$^+$: 224.12812; found: 224.12803.



8c

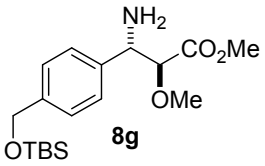
(2*S*,3S)-Methyl 3-amino-2-methoxy-3-(4-methoxyphenyl)propanoate (8c). A solution of azide **19c** (0.100 g, 0.377 mmol) in MeOH (3 mL) was hydrogenated at room temperature for 5 h to provide 0.089 g (98%) of amine **8c** as a slightly yellow oil. R_f (petroleum ether/EtOAc, 3:7) 0.15; $[\alpha]^{20}_D$ = –8.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 2H, NH_2), 3.36 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.93 (d, *J* = 5.3 Hz, 1H, 2-H), 4.21 (d, *J* = 5.6 Hz, 1H, 3-H), 6.83 (d, *J* = 8.7 Hz, 2H, Ar), 7.21 (d, *J* = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7 (OCH_3), 55.2 (OCH_3), 57.1 (C-3), 59.0 (OCH_3), 85.5 (C-2), 113.7 (C_{ar}), 128.0 (C_{ar}), 133.7 (C_{ar}), 158.9 (C_{ar}), 171.3 (CO); HRMS (ESI): *m/z*: calcd for $C_{12}H_{17}NO_4$ [*M*+Na]$^+$: 262.10498; found: 262.10496.



8d

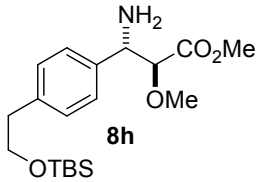
(2*S*,3*S*)-Methyl 3-amino-3-(4-fluorophenyl)-2-methoxypropanoate (8d). A solution of azide **19d** (0.239 g, 0.944 mmol) in MeOH (10 mL) was hydrogenated at room temperature for 5 h to provide 0.212 g (99%) of amine **8d** as a colorless oil. R_f (petroleum ether/EtOAc, 3:7) 0.24; $[\alpha]^{20}_D$ = –5.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81 (bs, 2H, NH_2), 3.37 (s, 3H, OCH_3), 3.64 (s,

3H, OCH_3), 3.94 (d, J = 5.3 Hz, 1H, 2-H), 4.26 (d, J = 5.6 Hz, 1H, 3-H), 6.85–7.04 (m, 2H, Ar), 7.24–7.31 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7 (OCH_3), 57.0 (C-3), 59.0 (OCH_3), 85.2 (C-2), 115.2 (d, J = 21.2 Hz, C_{ar}), 128.6 (d, J = 8.1 Hz, C_{ar}), 137.14 (d, J = 3.7 Hz, Car), 162.2 (d, J = 245.9 Hz, C_{ar}), 171.1 (CO); HRMS (ESI): *m/z*: calcd for $C_{11}H_{14}FNO_3$ [*M*+Na]$^+$: 228.10305; found: 228.10286.



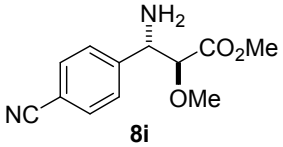
8g

(2*S*,3*S*)-Methyl 3-amino-3-(4-((*tert*-butyldimethylsilyloxy)methyl)phenyl)-2-methoxypropanoate (8g). A solution of azide **19g** (74.0 mg, 0.195 mmol) in MeOH (2 mL) was hydrogenated at room temperature for 2 h to provide 68 mg (99%) of amine **8g** as a colorless oil. Longer reaction times might cause reductive cleavage of the benzylic C–O bond. $[\alpha]^{20}_D$ = –6.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H, $SiCH_3$), 0.92 (s, 9H, $C(CH_3)_3$), 1.70 (bs, 2H, NH_2), 3.37 (s, 3H, OCH_3), 3.64 (s, 3H, CO_2CH_3), 3.96 (d, J = 5.6, 1H, 2-H), 4.25 (d, J = 5.6 Hz, 1H, 3-H), 4.70 (s, 2H, CH_2O), 7.26 (s, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 18.4 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 51.7 (OCH_3), 57.5 (C-3), 59.0 (OCH_3), 64.7 (CH_2Ar), 85.4 (C-2), 126.0 (C_{ar}), 126.8 (C_{ar}), 131.2 (C_{ar}), 140.7 (C_{ar}), 171.3 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{18}H_{31}NO_4Si$ [*M*+H]$^+$: 354.20951; found: 354.20953.



8h

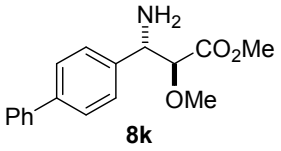
(2*S*,3*S*)-Methyl 3-amino-3-(4-(2-(*tert*-butyldimethylsilyloxy)ethyl)phenyl)-2-methoxypropanoate (8h). A solution of azide **19h** (0.566 g, 1.44 mmol) in MeOH (7 mL) was hydrogenated at room temperature overnight to provide 0.527 g (99%) of amine **8h** as a colorless oil. $[\alpha]^{20}_D$ = –6.4 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03 (s, 6H, $SiCH_3$), 0.86 (s, 9H, $C(CH_3)_3$), 1.73 (bs, 2H, NH_2), 2.78 (t, J = 7.1 Hz, 2H, $ArCH_2$), 3.36 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.77 (t, J = 7.1 Hz, 2H, CH_2O), 3.95 (d, J = 5.7 Hz, 1H, 2-H), 4.23 (d, J = 5.7 Hz, 1H, 3-H), 7.14 (d, J = 8.1 Hz, 2H, Ar), 7.21 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 39.2 ($ArCH_2$), 51.7 (OCH_3), 57.4 (C-3), 59.0 (OCH_3), 64.4 (CH_2O), 85.4 (C-2), 126.8 (C_{ar}), 129.1 (C_{ar}), 138.5 (C_{ar}), 139.4 (C_{ar}), 171.3 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{19}H_{33}NO_4Si$ [*M*+H]$^+$: 368.22516; found: 368.22538.



8i

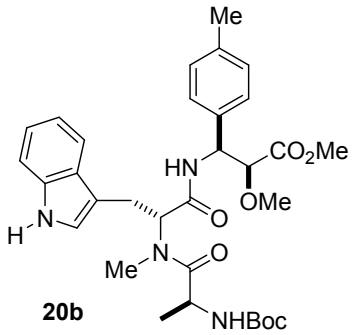
(2*S*,3*S*)-Methyl 3-amino-3-(4-cyanophenyl)-2-methoxypropanoate (8i). A solution of azide **19i** (43.7 mg, 0.168 mmol) in MeOH (0.9 mL) was hydrogenated at room temperature for 4 h to provide 33.6 mg (85%) of amine **8i** as a colorless oil. $[\alpha]^{20}_D$ = –13.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (bs, 2H, NH_2), 3.37 (s, 3H, OCH_3), 3.63 (s, 3H, CO_2CH_3), 3.94 (d, J =

5.4 Hz, 1H, 2-H), 4.31 (d, *J* = 5.4 Hz, 1H, 3-H), 7.41 (d, *J* = 8.3 Hz, 2H, Ar), 7.58 (d, *J* = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.8 (OCH_3), 57.4 (C-3), 59.0 (OCH_3), 84.7 (C-2), 111.4, 118.7, 127.9 (C_{ar}), 132.0 (C_{ar}), 146.8 (C_{ar}), 170.6 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{12}H_{14}N_2O_3$ $[M+H]^+$: 235.10772; found: 235.10763.



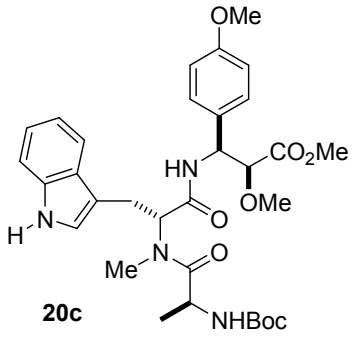
8k

(2*S*,3*S*)-Methyl 3-amino-3-(4-cyanophenyl)-2-methoxypropanoate (8k). A solution of azide **19k** (0.330 g, 1.06 mmol) in MeOH (5 mL) was hydrogenated at room temperature overnight to provide 0.292 g (97%) of amine **8k** as a colorless oil which solidified on standing. R_f (EtOAc) 0.3, (CH_2Cl_2/MeOH 10:1) 0.53; $[\alpha]^{20}_D$ = –7.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (bs, 2H, NH_2), 3.42 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 4.05 (d, *J* = 5.3 Hz, 1H, 2-H), 4.34 (d, *J* = 5.3 Hz, 1H, 3-H), 7.30–7.34 (m, 1H, Ar), 7.37–7.44 (m, 4H, Ar), 7.53–7.58 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.8 (OCH_3), 57.3 (C-3), 59.2 (OCH_3), 85.1 (C-2), 127.0 (C_{ar}), 127.1 (C_{ar}), 127.2 (C_{ar}), 127.5 (C_{ar}), 128.7 (C_{ar}), 140.1 (C_{ar}), 140.5 (C_{ar}), 140.7 (C_{ar}), 171.1 (CO_2CH_3); HMRS (ESI): *m/z*: calcd for $C_{17}H_{19}NO_3$ $[M+H]^+$: 308.12571; found: 308.125706.



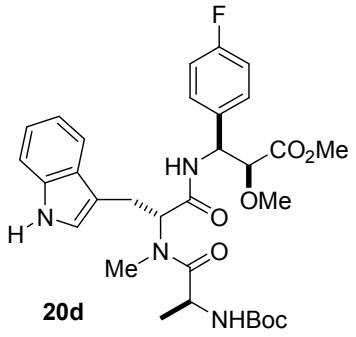
20b

Tripeptide 20b (Me). To a solution of amine **8b** (40 mg, 0.179 mmol, 1 equiv) in DMF (4 mL) were added acid **6** (70 mg, 0.179 mmol), HOBt (36 mg, 0.269 mmol, 1.5 equiv), *i*Pr_2NEt (0.091 mL, 0.537 mmol, 3 equiv). At 0 °C TBTU (84 mg, 0.269 mmol, 1.5 equiv) was added and the reaction was stirred for 2–3 h at room temperature. The mixture was diluted with water (4 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with 1N HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 1:1) gave tripeptide **20b** (80 mg, 75%) as a white foam. R_f (petroleum ether/EtOAc, 1:1) 0.20; $[\alpha]^{20}_D$ = +12.6 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.41 (s, 9H, $C(CH_3)_3$), 2.28 (s, 3H, $ArCH_3$), 2.94 (s, 3H, NCH_3), 3.19–3.29 (m, 1H, CH_2), 3.31–3.36 (m, 1H, CH_2), 3.36 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 4.07 (d, *J* = 4.8 Hz, 1H, C*H*OCH_3), 4.46–4.55 (m, 1H, Ala CH), 5.38 (dd, *J* = 8.7, 4.8 Hz, 1H, β-Tyr CH), 5.43 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.54 (dd, *J* = 9.9, 6.4 Hz, 1H, Trp CH), 6.90 (s, 1H, Trp H_{Ar}), 6.98–7.18 (m, 7H, β-Tyr H_{Ar}, Trp Har, β-Tyr NH), 7.29 (d, *J* = 8.1 Hz, 1H Trp H_{Ar}), 7.57 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 8.33 (bs, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (Ala CH_3), 21.1 ($ArCH_3$), 23.3 (CH_2), 28.3 ($C(CH)_3$), 30.7 (NCH_3), 46.7 (Ala CH), 51.8 (OCH_3), 53.9 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH_3), 79.5 ($C(CH)_3$), 82.4 ($CHOCH_3$), 110.6 (Trp C_{ar}), 111.1 (Trp C_{ar}), 118.4 (Trp C_{ar}), 119.4 (Trp C_{ar}), 122.0 (Trp C_{ar}), 122.2 (Trp C_{ar}), 127.2 (Trp C_{ar}), 127.3 (β-Tyr C_{ar}), 129.1 (β-Tyr C_{ar}), 133.6 (β-Tyr C_{ar}), 136.1 (Trp C_{ar}), 137.6 (Trp C_{ar}), 155.1 (CO), 169.3 (CO), 170.1 (CO), 174.3 (CO); HRMS (ESI): *m/z*: calcd for $C_{32}H_{42}N_4O_7$ $[M+Na]^+$: 617.29457; found: 617.29448.



20c

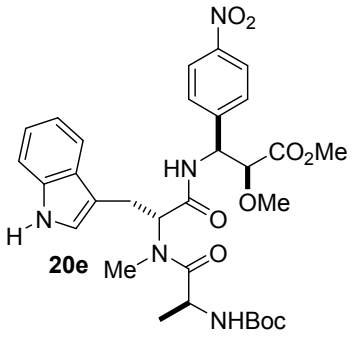
Tripeptide 20c (OMe). To a solution of amine **8c** (89 mg, 0.372 mmol, 1 equiv) in DMF (7 mL) were added acid **6** (145 mg, 0.372 mmol), HOBt (75 mg, 0.558 mmol, 1.5 equiv), *i*Pr_2NEt (0.091 mL, 0.537 mmol, 3 equiv). At 0 °C TBTU (174 mg, 0.558 mmol, 1.5 equiv) was added and the reaction was stirred for 2–3 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1N HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 1:1) gave tripeptide **20c** (175 mg, 77%) as a white foam. R_f (petroleum ether/EtOAc, 1:1) 0.32; $[\alpha]^{20}_D$ = +17.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 2.95 (s, 3H, NCH_3), 3.23 (dd, *J* = 15.5, 9.9 Hz, 1H, CH_2), 3.27–3.34 (m, 1H, CH_2), 3.37 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.74 (OCH_3), 4.06 (d, *J* = 5.1 Hz, 1H, C*H*OCH_3), 4.45–4.56 (m, 1H, Ala CH), 5.35 (dd, *J* = 8.5, 5.0 Hz, 1H, β-Tyr CH), 5.41 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.53 (dd, *J* = 9.8, 6.5 Hz, 1H, Trp CH), 6.77 (d, *J* = 8.9 Hz, 2H, β-Tyr H_{ar}), 6.89 (s, 1H, Trp H_{ar}), 7.04–7.12 (m, 2H, β-Tyr NH, Trp H_{ar}), 7.14 (d, *J* = 7.1 Hz, 2H, β-Tyr H_{ar}), 7.12–7.18 (m, 1H, Trp H_{ar}), 7.29 (d, *J* = 8.1 Hz, 1H Trp H_{ar}), 7.57 (d, *J* = 7.9 Hz, 1H, Trp H_{ar}), 8.26 (bs, 1H, Trp NH); ^{13}C NMR (100 MHz, CDCl): δ = 18.0 (Ala CH_3), 23.3 (CH_2), 28.3 (C(*C*H)$_3$), 30.8 (NCH_3), 46.7 (Ala CH), 51.8 (OCH_3), 53.7 (β-Tyr CH), 55.1 (OCH_3), 56.7 (Trp CH), 59.2 (OCH_3), 79.6 (*C*$(CH)_3$), 82.4 (*C*HOCH_3), 110.7 (Trp C_{ar}), 111.1 (Trp C_{ar}), 113.8 (β-Tyr C_{ar}), 118.5 (Trp C_{ar}), 119.4 (Trp C_{ar}), 122.0 (Trp C_{ar}), 122.2 (Trp C_{ar}), 127.2 (Trp C_{ar}), 128.7 (β-Tyr C_{ar}), 128.8 (β-Tyr C_{ar}), 136.1 (Trp C_{ar}), 155.1 (CO), 159.2 (β-Tyr C_{ar}), 169.3 (CO), 170.1 (CO), 174.3 (CO); HRMS (ESI): *m/z*: calcd for $C_{32}H_{42}N_4O_8$ [*M*+Na]$^+$: 633.28949; found: 633.28983.



20d

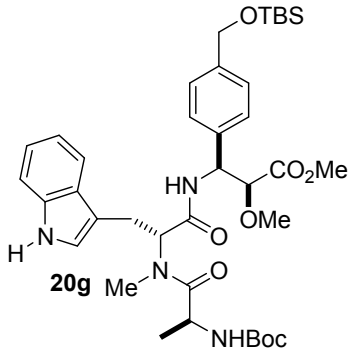
Tripeptide 20d (F). To a solution of amine **8d** (100 mg, 0.440 mmol, 1 equiv) in DMF (8 mL) were added acid **6** (171 mg, 0.440 mmol), HOBt (89 mg, 0.660 mmol, 1.5 equiv), *i*Pr_2NEt (0.225 mL, 1.32 mmol, 3 equiv). At 0 °C TBTU (206 mg, 0.660 mmol, 1.5 equiv) was added and the reaction was stirred for 2–3 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1N HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography

(petroleum ether/EtOAc, 1:1) gave tripeptide **20d** (180 mg, 68%) as a white foam. R_f (petroleum ether/EtOAc, 1:1) 0.26; $[\alpha]^{20}_D$ = +15.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.6 Hz, 3H, Ala CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 2.96 (s, 3H, NCH_3), 3.21 (dd, *J*=15.6, 9.8 Hz, 1H, CH_2), 3.32–3.40 (m, 1H, CH_2), 3.37 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 4.06 (d, *J* = 4.8 Hz, 1H, C*H*OCH_3), 4.45–4.55 (m, 1H, Ala CH), 5.33–5.41 (m, 2H, β-Tyr CH, Ala NH), 5.52 (dd, *J* = 9.7, 6.6 Hz, 1H, Trp CH), 6.90 (s, 1H, Trp H_{ar}), 6.90–6.97 (m, 2H, β-Tyr H_{ar}), 7.07–7.22 (m, β-Tyr H_{ar}, Trp H_{ar}, β-Tyr NH), 7.31 (d, *J* = 7.9 Hz, 1H Trp H_{ar}), 7.58 (d, *J* = 7.9 Hz, 1H, Trp H_{ar}), 8.11 (bs, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (Ala CH_3), 23.4 (CH_2), 28.3 (C(*C*H)$_3$), 30.8 (NCH_3), 46.7 (Ala CH), 51.9 (OCH_3), 53.6 (β-Tyr CH), 56.7 (Trp CH), 59.2 (OCH_3), 79.6 (*C*$(CH)_3$), 82.2 (*C*HOCH_3), 110.7 (Trp C_{ar}), 111.1 (Trp C_{ar}), 115.3 (d, *J* = 21.2 Hz), 118.5 (Trp C_{ar}), 119.5 (Trp C_{ar}), 122.1 (Trp C_{ar}), 127.2 (Trp C_{ar}), 129.4 (d, *J* = 8.8 Hz, β-Tyr C_{ar}), 132.7 (d, *J* = 3.7 Hz, β-Tyr C_{ar}), 136.1 (Trp C_{ar}), 155.2 (CO), 163.4 (d, *J* = 264.3 Hz, β-Tyr C_{ar}), 169.4 (CO), 169.9 (CO), 174.4 (CO); HRMS (ESI): *m/z*: calcd for $C_{31}H_{39}FN_4O_7$ $[M+Na]^+$: 621.26950; found: 621.26986.



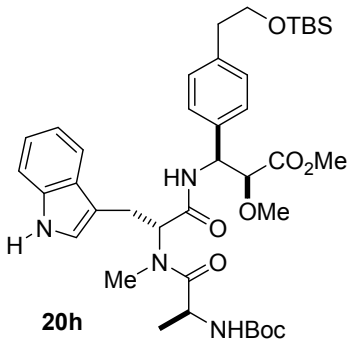
Reduction of azide 19e and coupling of amine 8e with acid 6 to tripeptide 20e (NO_2). A solution of azide **19e** (89.6 mg, 0.32 mmol) and PPh_3 (92.2 mg, 0.352 mmol, 1.1 equiv) in of THF (1 mL) was stirred at 40–50 °C for 1 h for clean and complete conversion to the corresponding iminophosphorane (TLC control: CH_2Cl_2/MeOH/NH_3, 10:1:0.1, R_f 0.5 for the iminophosphorane). Selected ^{1}H NMR (400 MHz, $CDCl_3$) data for the iminophosphorane: δ = 7.91 (d, 2H), 3.67 (s, 3H), 3.13 (s, 3H). Then water (0.1 mL) was added and the mixture was further stirred at 40–50 °C for ~8 h. Because the R_f values of the iminophosphorane, Ph_3P=O and the resulting amine were all the same, the reaction progress was conveniently monitored by analyzing small evaporated probes taken from the reaction mixture by NMR. Selected ^{1}H NMR (400 MHz, $CDCl_3$) data for the amine: δ = 8.15 (d, 2H), 3.65 (s, 3H), 3.39 (s, 3H). When appropriately clean and high (~86%) conversion was achieved, the mixture was evaporated to yield 0.166 g of a sticky oil, containing ~36% w/w amine **8e** (assuming the conversion was 80% as the lowest). Then, to a solution of this crude mixture (0.108 mg), containing amine **8e** (approx. 38.9 mg, 0.153 mmol, 1.24 equiv of the amine) in DMF (2.3 mL) were added acid **6** (47.7 mg, 0.123 mmol), HOBt (24.9 mg, 0.184 mmol, 1.5 equiv), *i*Pr_2NEt (0.064 mL, 0.369 mmol, 3 equiv). At –10 °C TBTU (59 mg, 0.184 mmol, 1.5 equiv) was added and the reaction was stirred for 5–6 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with 1N $NaHSO_4$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 2:1) gave tripeptide **20e** (58.7 mg, 76%) as a white foam. R_f (petroleum ether/EtOAc, 2:1) 0.48. $[\alpha]^{20}_D$ = +4.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.40 (s, 9H, *t*Bu), 2.98 (s, 3H, NCH_3), 3.17 (dd, *J* = 15.5, 9.4 Hz, 1H, CH_2), 3.38 (s, 3H, OCH_3), 3.38 (m, 1H, CH_2), 3.61 (s, 3H, CO_2CH_3), 4.07 (d, *J* = 5.1 Hz, 1H, C*H*OCH_3), 4.48–4.54 (m, 1H, Ala CH), 5.33 (d, *J* = 7.4 Hz, 1H, Ala NH), 5.44 (dd, *J* = 8.1, 5.1 Hz, 1H, β-Tyr CH), 5.53 (dd, *J* = 8.9, 7.4 Hz, 1H, Trp CH), 6.89 (s, 1H, Trp H_{Ar}),

7.08 (ddd, J = 7.9, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.16 (ddd, J = 7.9, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.21 (d, J = 8.1 Hz, 1H, β-Tyr NH), 7.31 (d, J = 7.9 Hz, 1H, Trp H_{Ar}), 7.34 (d, J = 8.3 Hz, 2H, Ar), 7.57 (d, J = 7.9 Hz, 1H, Trp H_{Ar}), 8.06 (d, J = 8.3 Hz, 2H, Ar), 8.21 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (Ala CH_3), 23.5 (CH_2), 28.3 (C(CH_3)$_3$), 30.9 (NCH_3), 46.7 (Ala CH), 52.1 (OCH_3), 53.8 (β-Tyr CH), 56.8 (Trp CH), 59.3 (OCH_3), 79.7 (C(CH$_3$)$_3$), 81.8 (CHOCH$_3$), 110.5 (quat. Trp), 111.2, 118.5, 119.5, 122.2 (2C, Trp), 123.4 (2C, Ar), 127.1 (quat. Trp), 128.7 (2C, Ar), 136.1 (quat. Trp), 144.3 (quat. Ar), 147.5 (quat. Ar), 155.2 (Boc), 169.5, 169.6, 174.5; HMRS (ESI): *m/z*: calcd for $C_{31}H_{39}N_5O_9$ [M+Na]$^+$: 648.26400; found: 648.26502.



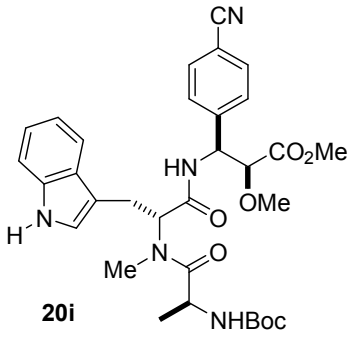
20g

Tripeptide 20g (CH$_2$OTBS). To a solution of amine **8g** (52.1 mg, 0.147 mmol, 1.2 equiv) in DMF (2.3 mL) were added acid **6** (47.7 mg, 0.123 mmol), HOBt (24.9 mg, 0.184 mmol, 1.5 equiv), iPr$_2$NEt (0.064 mL, 3 equiv). At –10 °C TBTU (59 mg, 0.184 mmol, 1.5 equiv) was added and the reaction was stirred for 5–6 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1N $NaHSO_4$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 1:1 to 1:2) gave tripeptide **20g** (78.8 mg, 88%) as a white foam. R_f (petroleum ether/EtOAc, 1:2) 0.5; $[\alpha]^{20}_D$ = +11.1 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiCH_3$), 0.93 (s, 12H, tBu, Ala CH_3), 1.41 (s, 9H, tBu), 2.97 (s, 3H, NCH_3), 3.19 (dd, J = 15.4, 9.7 Hz, 1H, CH_2), 3.34 (dd, J = 15.4, 6.8 Hz, 1H, CH_2), 3.37 (s, 3H, OCH_3), 3.58 (s, 3H, CO_2CH_3), 4.06 (d, J = 5.1 Hz, 1H, CHOCH$_3$), 4.49–4.56 (m, 1H, Ala CH), 4.68 (s, 2H, OCH_2), 5.39 (dd, J = 8.8, 5.1 Hz, 1H, β-Tyr CH), 5.43 (d, J = 7.8 Hz, 1H, Ala NH), 5.50 (dd, J = 9.7, 6.8 Hz, 1H, Trp CH), 6.82 (d, 1H, Trp H_{Ar}), 7.04 (d, J = 8.8 Hz, 1H, β-Tyr NH), 7.07–7.22 (m, 6H, Ar, Trp H_{Ar}), 7.29 (d, J = 7.8 Hz, 1H, Trp H_{Ar}), 7.57 (d, J = 7.8 Hz, 1H, Trp H_{Ar}), 8.21 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 18.1 (C(CH$_3$)$_3$), 18.4 (Ala CH_3), 23.4 (CH_2), 25.9 (C(CH$_3$)$_3$), 28.3 (C(CH$_3$)$_3$), 30.8 (NCH_3), 46.7 (Ala CH), 51.8 (OCH_3), 54.0 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH_3), 64.7 (CH_2O), 79.5 (C(CH$_3$)$_3$), 82.3 (CHOCH$_3$), 110.5 (quat. Trp), 111.1, 118.4, 119.4, 122.0, 122.3, 126.2 (2C, Ar), 127.1 (quat. Trp), 127.5 (2C, Ar), 135.5, 136.1 (quat. Trp), 140.9, 155.1 (Boc), 169.3, 170.0, 174.2; HMRS (ESI): *m/z*: calcd for $C_{38}H_{56}N_4O_8Si$ [M+Na]$^+$: 747.37596; found: 747.37575.



20h

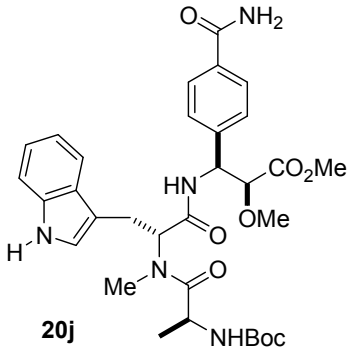
Tripeptide 20h (CH_2CH_2OTBS). To a solution of amine **8h** (68 mg, 0.185 mmol, 1.2 equiv) in DMF (2.9 mL) were added acid **6** (60 mg, 0.154 mmol), HOBt (31 mg, 0.231 mmol, 1.5 equiv), *i*Pr_2NEt (0.081 mL, 0.462 mmol, 3 equiv). At –10 °C TBTU (74 mg, 0.231 mmol, 1.5 equiv) was added and the reaction was stirred for 5–6 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with 1N $NaHSO_4$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 1:1 to 1:2) gave tripeptide **20h** (97.7 mg, 86%) as a white foam. R_f (petroleum ether/EtOAc, 1:2) 0.55; (petroleum ether/EtOAc, 1:1) 0.34; $[\alpha]^{20}_D$ = +10.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 (s, 6H, $SiCH_3$), 0.86 (s, 9H, *t*Bu), 0.94 (s, *J* = 6.8 Hz, 3H, Ala CH_3), 1.41 (s, 9H, *t*Bu), 2.76 (t, *J* = 6.8 Hz, 2H, CH_2Ar), 2.97 (s, 3H, NCH_3), 3.20 (dd, *J* = 15.4, 9.6 Hz, 1H, CH_2), 3.34 (dd, *J* = 15.4, 6.8 Hz, 1H, CH_2), 3.36 (s, 3H, OCH_3), 3.58 (s, 3H, CO_2CH_3), 3.79 (t, *J* = 6.8 Hz, 2H, OCH_2), 4.05 (d, *J* = 5.1 Hz, 1H, C*H*OCH_3), 4.49–4.56 (m, 1H, Ala CH), 5.37 (dd, *J* = 8.7, 5.8 Hz, 1H, β-Tyr CH), 5.44 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.49 (dd, *J* = 9.6, 6.8 Hz, 1H, Trp CH), 6.82 (s, 1H, Trp H_{Ar}), 7.00 (d, *J* = 8.7 Hz, 1H, β-Tyr NH), 7.05–7.16 (m, 6H, Ar, Trp H_{Ar}), 7.28 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 7.57 (d, *J* = 7.6 Hz, 1H, Trp H_{Ar}), 8.31 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), 18.1 (*C*$(CH_3)_3$), 18.3 (Ala CH_3), 23.5 (CH_2), 25.9 (C(*C*$H_3)_3$), 28.3 (C(*C*$H_3)_3$), 30.8 (NCH_3), 39.2 (CH_2Ar), 46.7 (Ala CH), 51.8 (OCH_3), 53.9 (β-Tyr CH), 56.6 (Trp CH), 59.1 (OCH_3), 64.3 (CH_2O), 79.5 (*C*$(CH_3)_3$), 82.3 (*C*HOCH_3), 110.4 (quat. Trp), 111.1, 118.4, 119.3, 121.9, 122.3, 127.1 (quat. Trp), 127.4 (2C, Ar), 129.2 (2C, Ar), 134.7, 136.1 (quat. Trp), 138.8, 155.1 (Boc), 169.3, 170.0, 174.2; HMRS (ESI): *m/z*: calcd for $C_{39}H_{58}N_4O_8Si$ $[M+Na]^+$: 761.39161; found: 761.39196.



20i

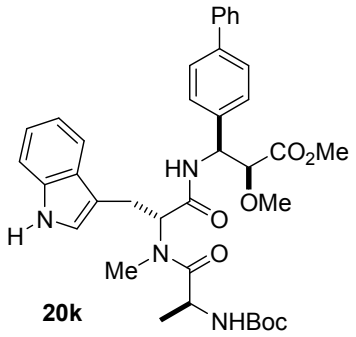
Tripeptide 20i (CN). To a solution of amine **8i** (68 mg, 0.154 mmol, 1.2 equiv) in DMF (2.4 mL) were added acid **6** (50.2 mg, 0.129 mmol), HOBt (26.1 mg, 0.193 mmol, 1.5 equiv), *i*Pr_2NEt (0.068 mL, 0.387 mmol, 3 equiv). At –10 °C TBTU (62.1 mg, 0.193 mmol, 1.5 equiv) was added and the reaction was stirred for 5–6 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with 1N $NaHSO_4$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 1:1 to 1:2) gave tripeptide **8i** (67.1 mg, 86%) as a white

foam. $[\alpha]^{20}_D$ = +4.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.40 (s, 9H, *t*Bu), 2.96 (s, 3H, NCH_3), 3.24 (dd, *J* = 15.4, 9.6 Hz, 1H, CH_2), 3.37 (s, 3H, OCH_3), 3.38 (dd, *J* = 15.4, 6.8 Hz, 1H, CH_2), 3.60 (s, 3H, CO_2CH_3), 4.05 (d, *J* = 5.1 Hz, 1H, C*H*OCH_3), 4.47–4.53 (m, 1H, Ala CH), 5.33 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.39 (dd, *J* = 8.3, 5.1 Hz, 1H, β-Tyr CH), 5.52 (dd, *J* = 9.6, 6.8 Hz, 1H, Trp CH), 6.89 (s, 1H, Trp H_{Ar}), 7.09 (ddd, *J* = 7.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.16 (ddd, *J* = 7.8, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.20 (d, *J* = 8.3 Hz, 1H, β-Tyr NH), 7.29 (d, *J* = 8.3 Hz, 2H, Ar), 7.31 (d, *J* = 7.1 Hz, 1H, Trp H_{Ar}), 7.51 (d, *J* = 8.3 Hz, 2H, Ar), 7.56 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 8.22 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (Ala CH_3), 23.4 (CH_2), 28.3 (C(*C*H_3)$_3$), 30.8 (NCH_3), 46.7 (Ala CH), 52.1 (OCH_3), 54.0 (β-Tyr CH), 56.8 (Trp CH), 59.3 (OCH_3), 79.7 (*C*$(CH_3)_3$), 81.8 (*C*HOCH_3), 110.5 (quat. Trp), 111.1, 111.7 (quat.), 118.4, 118.6 (quat.), 119.5, 122.2 (2C), 127.1 (quat. Trp), 128.5 (2C, Ar), 132.1 (2C, Ar), 136.1 (quat. Trp), 142.3, 155.2 (Boc), 169.6 (2C), 174.5.



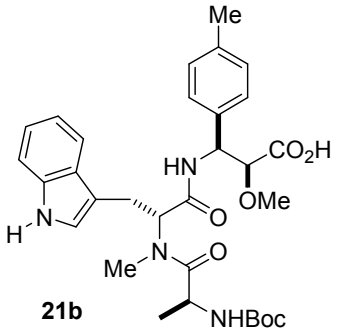
20j

Tripeptide 20j ($CONH_2$). To a solution of amine **8j** (40.4 mg, 0.160 mmol, 1.6 equiv) in DMF (2 mL) were added acid **6** (38.9 mg, 0.100 mmol, 1 equiv), HOBt (20.3 mg, 0.150 mmol, 1.5 equiv), *i*Pr_2NEt (0.052 mL, 0.3 mmol, 3 equiv). At –10 °C TBTU (48.2 mg, 0.150 mmol, 1.5 equiv) was added and the reaction was stirred for 5–6 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with 1N $NaHSO_4$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH, 10:1) gave tripeptide **20j** contaminated with DMF and TMU, repeated chromatography using EtOAc afforded clean product (46.1 mg, 74%) as a white foam. R_f (EtOAc) 0.25; $[\alpha]^{20}_D$ = +5.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.40 (s, 9H, *t*Bu), 3.01 (s, 3H, NCH_3), 3.12 (dd, *J* = 15.3, 8.7 Hz, 1H, CH_2), 3.35 (s, 3H, OCH_3), 3.37 (dd, *J* = 15.4, 7.4 Hz, 1H, CH_2), 3.58 (s, 3H, CO_2CH_3), 4.05 (d, *J* = 4.8 Hz, 1H, C*H*OCH_3), 4.51–4.57 (m, 1H, Ala CH), 5.37 (dd, *J* = 8.1, 5.1 Hz, 1H, β-Tyr CH), 5.47 (d, *J* = 7.4 Hz, 1H, Ala NH), 5.52 (dd, *J* = 8.1, 7.9 Hz, 1H, Trp CH), 6.02 (s, 1H, $CONH_2$), 6.36 (s, 1H, $CONH_2$), 6.78 (s, 1H, Trp H_{Ar}), 7.07 (ddd, *J* = 7.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.12–7.16 (m, 2H, Ar, Trp H_{Ar}), 7.25 (d, *J* = 8.1 Hz, 1H, β-Tyr NH), 7.28 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 7.58 (app d, *J* = 7.3 Hz, 3H, Ar, Trp H_{Ar}), 8.49 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.07 (Ala CH_3), 23.8 (CH_2), 28.3 (C(*C*H_3)$_3$), 30.9 (NCH_3), 46.7 (Ala CH), 52.0 (OCH_3), 54.1 (β-Tyr CH), 56.8 (Trp CH), 59.2 (OCH_3), 79.7 (*C*$(CH_3)_3$), 82.0 (*C*HOCH_3), 110.2 (quat. Trp), 111.3, 118.4, 119.4 (quat.), 122.0, 122.5, 127.1 (quat. Trp), 127.4 (2C, Ar), 127.7 (2C, Ar), 132.9, 136.2 (quat. Trp), 140.9, 155.2 (Boc), 169.3, 169.6, 169.9, 174.4; HMRS (ESI): *m/z*: calcd for $C_{32}H_{41}N_5O_8$ [*M*+Na]$^+$: 646.28473; found: 646.28443.



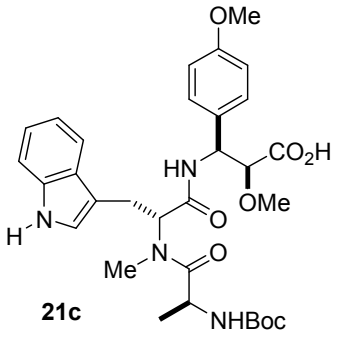
20k

Tripeptide 20k (Ph). To a solution of amine **8k** (52.0 mg, 0.182 mmol, 1.2 equiv) in DMF (2.9 mL) were added acid **6** (59.1 mg, 0.152 mmol), HOBt (31 mg, 0.228 mmol, 1.5 equiv), *i*Pr_2NEt (0.08 mL, 0.456 mmol, 3 equiv). At –10 °C TBTU (73 mg, 0.228 mmol, 1.5 equiv) was added and the reaction was stirred for 5–6 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1N $NaHSO_4$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 1:1 to 1:2) gave tripeptide **20k** (83.3 mg, 83%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3H, Ala CH_3), 1.42 (s, 9H, *t*Bu), 2.97 (s, 3H, NCH_3), 3.24 (dd, *J* = 15.8, 9.8 Hz, 1H, CH_2), 3.35–3.40 (m, 1H, CH_2), 3.35 (s, 3H, OCH_3), 3.62 (s, 3H, CO_2CH_3), 4.11 (d, *J* = 4.8 Hz, 1H, C*H*OCH_3), 4.50–4.57 (m, 1H, Ala CH), 5.44 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.47 (dd, *J* = 8.4, 4.8 Hz, 1H, β-Tyr CH), 5.56 (dd, *J* = 9.8, 6.4 Hz, 1H, Trp CH), 6.91 (d, *J* = 1.5 Hz, 1H, Trp H_{ar}), 7.08–7.19 (m, 3H, Trp H_{Ar}, β-Tyr NH), 7.28–7.34 (m, 4H), 7.42 (t, 2H), 7.48 (d, *J* = 8.3 Hz, 2H, Ar), 7.54 (d, *J* = 7.1 Hz, 2H, Ar), 7.59 (d, *J* = 7.8 Hz, 1H, Trp H_{ar}), 8.25 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (Ala CH_3), 23.3 (CH_2), 28.3 (C(*C*H_3)$_3$), 30.8 (NCH_3), 46.7 (Ala CH), 51.9 (OCH_3), 53.9 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH_3), 79.6 (*C*(CH_3)$_3$), 83.1 (*C*HOCH_3), 110.6 (quat. Trp), 111.1, 118.5, 119.4, 122.0, 122.2, 127.0 (2C, Ar), 127.11 (2C, Ar), 127.16 (quat. Trp), 127.3 (2C, Ar), 127.9 (Ar), 128.7 (2C, Ar), 135.7, 136.1 (quat. Trp), 140.6, 140.7, 155.1 (Boc), 169.4, 170.0, 174.4.



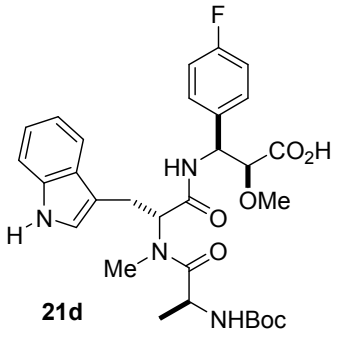
21b

Tripeptide acid 21b (Me). To a stirred solution of tripeptide ester **20b** (57.0 mg, 0.096 mmol) in 1,2-dichloroethane (1.5 mL) was added Me_3SnOH (87 mg, 0.480 mmol). After stirring for 5 h at 80 °C, TLC showed complete conversion and the reaction mixture was diluted with $KHSO_4$ (5% in water, 4 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21b** as a colorless foam.



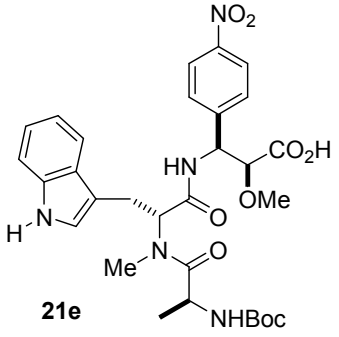
21c

Tripeptide acid 21c (OMe). To a stirred solution of tripeptide ester **20c** (0.135 g, 0.221 mmol) in 1,2-dichloroethane (3.5 mL) was added Me_3SnOH (160 mg, 0.884 mmol). After stirring for 5 h at 80 °C, TLC showed complete conversion and the reaction mixture was diluted with $KHSO_4$ (5% in water, 6 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21c** as a colorless foam.



21d

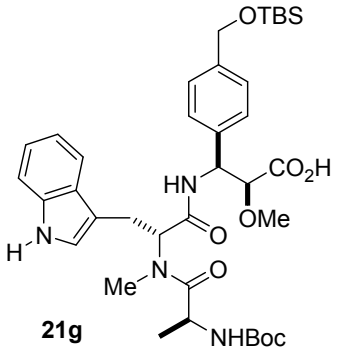
Tripeptide acid 21d (F). To a stirred solution of tripeptide ester **20d** (0.057 g, 0.095 mmol) in 1,2-dichloroethane (1.5 mL) was added Me_3SnOH (86 mg, 0.475 mmol). After stirring for 5 h at 80 °C, TLC showed complete conversion and the reaction mixture was diluted with $KHSO_4$ (5% in water, 4 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21d** as a colorless foam.



21e

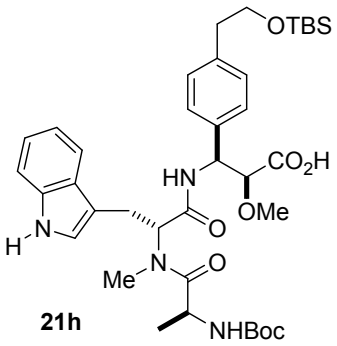
Tripeptide acid 21e (NO_2). To a solution of methyl ester **20e** (55.3 mg, 0.0884 mmol) in THF (0.4 mL) were added water (0.6 mL), methanol (0.3 mL) and NaOH (7.5 mg, 0.188 mmol, 2.1 equiv). The initial biphasic mixture became homogeneous with progressing saponification. After being stirred for 1 h at room temperature until complete conversion (controlled by TLC), the mixture was diluted with water (5 mL) and ethyl acetate (8 mL). It was carefully acidified with 1M $NaHSO_4$ to pH ~ 2 before the layers were separated and the aqueous phase extracted once with ethyl acetate (8

mL). The combined organic layers were washed with water, saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21e** as a colorless foam. R_f (EtOAc/AcOH, 100:1) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.39 (s, 9H, *t*-Bu), 2.93 (s, 3H, NCH_3), 3.18 (dd, *J* = 15.3, 9.9 Hz, 1H, CH_2), 3.28–3.34 (m, 1H, CH_2), 3.34 (s, 3H, OCH_3), 3.98 (d, *J* = 6.3 Hz, 1H, C*H*OCH_3), 4.42–4.49 (m, 1H, Ala CH), 5.40 (dd, *J* = 7.6, 7.1 Hz, 1H, β-Tyr CH), 5.46 (d, *J* = 7.4 Hz, 1H, Ala NH), 5.59 (dd, *J* = 9.9, 7.4 Hz, 1H, Trp CH), 6.88 (s, 1H, Trp H_{Ar}), 7.05 (app t, *J* = 7.0 Hz, 1H, Trp H_{Ar}), 7.13 (app t, *J* = 7.0 Hz, 1H, Trp H_{Ar}), 7.21 (d, *J* = 8.6 Hz, 1H, β-Tyr NH), 7.28 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 7.41 (d, *J* = 8.4 Hz, 2H, Ar), 7.53 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 8.04 (d, *J* = 8.4 Hz, 2H, Ar), 8.36 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0 (Ala CH_3), 23.2 (CH_2), 28.3 (C(*C*H_3)$_3$), 30.6 (NCH_3), 46.6 (Ala CH), 54.0 (β-Tyr CH), 56.7 (Trp CH), 58.8 (OCH_3), 80.8 (*C*$(CH_3)_3$), 82.5 (*C*HOCH_3), 110.2 (quat. Trp), 111.2, 118.4, 119.5, 122.1, 122.3, 123.5 (2C, Ar), 127.1 (quat. Trp), 128.4 (2C, Ar), 136.1 (quat. Trp), 145.2 (quat. Ar), 147.4 (quat. Ar), 156.3 (Boc), 169.5, 170.7, 174.8; HMRS (ESI): *m/z*: calcd for $C_{30}H_{37}N_5O_9$ [*M*+Na]$^+$: 634.24835; found: 634.24819.



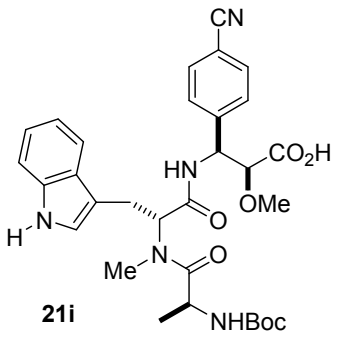
21g

Tripeptide acid 21g (CH_2OTBS). To a solution of methyl ester **20g** (75.5 mg, 0.104 mmol) in THF (0.4 mL) were added water (0.6 mL), methanol (0.3 mL) and NaOH (8.0 mg, 0.2 mmol, 1.9 equiv). The initial biphasic mixture became homogeneous with progressing saponification. After being stirred for 2 h at room temperature until complete conversion (controlled by TLC), the mixture was diluted with water (5 mL) and ethyl acetate (8 mL). It was carefully acidified with 1M $NaHSO_4$ to pH ~ 2 before the layers were separated and the aqueous phase extracted once with ethyl acetate (8 mL). The combined organic layers were washed with water, saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21g** as a colorless foam. Since the saponification was accompanied by partial cleavage of the silyl ether [R_f (EtOAc/AcOH, 100:1) 0.23 for deprotected acid] the crude material was purified by flash chromatography (EtOAc/petroleum ether/AcOH, 100:50:0.6) to provide the acid **21g** (61.3 mg, 82%) as a white foam. R_f (EtOAc/AcOH, 100:1) 0.57; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiCH_3$), 0.77 (d, *J* = 6.9 Hz, 1H, Ala CH_3), 0.93 (s, 9H, *t*-Bu), 1.41 (s, 9H, *t*-Bu), 2.92 (s, 3H, NCH_3), 3.20–3.32 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 4.03 (d, *J* = 5.9 Hz, 1H, C*H*OCH_3), 4.41–4.49 (m, 1H, Ala CH), 4.69 (s, 2H, OCH_2), 5.36–5.40 (m, 2H, β-Tyr CH, Ala NH), 5.60 (dd, *J* = 9.7, 6.6 Hz, 1H, Trp CH), 6.88 (s, 1H, Trp H_{Ar}), 6.97 (d, *J* = 9.2 Hz, 1H, β-Tyr NH), 7.07 (t, 1H, Trp H_{Ar}), 7.14 (t, *J* = 7.4 Hz, 1H, Trp H_{Ar}), 7.22–7.30 (d, 3H, Ar, Trp H_{Ar}), 7.56 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 8.24 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 16.9 (*C*$(CH_3)_3$), 18.4 (Ala CH_3), 22.9 (CH_2), 25.9 (C(*C*H_3)$_3$), 28.3 (C(*C*H_3)$_3$), 30.5 (NCH_3), 46.9 (Ala CH), 54.0 (β-Tyr CH), 56.6 (Trp CH), 58.8 (OMe), 64.6 (CH_2O), 80.6 (*C*$(CH_3)_3$), 83.3 (*C*HOCH_3), 110.2, 111.1, 118.4, 119.3, 121.9, 122.4, 126.2, 127.3 (3C), 136.0, 136.4, 140.9, 156.2 (Boc), 169.2, 171.0, 174.7. HMRS (ESI): *m/z*: calcd for $C_{37}H_{54}N_4O_8Si$ [*M*+Na]$^+$: 733.36031; found: 733.36067.



21h

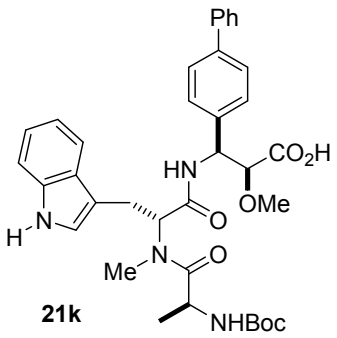
Tripeptide acid 21h (CH_2CH_2OTBS). To a solution of methyl ester **20h** (94.7 mg, 0.128 mmol) in THF (0.3 mL) were added water (0.7 mL), methanol (0.5 mL) and NaOH (10 mg, 0.25 mmol, 2 equiv). The initial biphasic mixture became homogeneous with progressing saponification. After being stirred for overnight at room temperature until complete conversion (controlled by TLC), the mixture was diluted with water (5 mL) and ethyl acetate (8 mL). It was carefully acidified with 1M $NaHSO_4$ to pH ~ 2 before the layers were separated and the aqueous phase extracted once with ethyl acetate (8 mL). The combined organic layers were washed with water, saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21h** as a colorless foam. Since the saponification was accompanied by partial cleavage of the silyl ether [R_f (EtOAc/AcOH, 100:1) 0.31 for deprotected acid] the crude material was purified by flash chromatography (EtOAc/petroleum ether/AcOH, 100:50:0.6) to provide the acid **21h** (74.2 mg, 80%) as a white foam; R_f (EtOAc/AcOH, 100:1) 0.62. In addition, 13.7 mg of the byproduct were isolated. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02 (s, 6H, $SiCH_3$), 0.79 (s, J = 7.1 Hz, 3H, Ala CH_3), 0.86 (s, 9H, *t*-Bu), 1.42 (s, 9H, *t*-Bu), 2.78 (t, J = 7.1 Hz, 2H, CH_2Ar), 2.93 (s, 3H, NCH_3), 3.20–3.32 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 3.78 (t, J = 7.1 Hz, 2H, OCH_2), 4.01 (d, J = 5.9 Hz, 1H, C*H*OCH_3), 4.42–4.49 (m, 1H, Ala CH), 5.30 (d, J = 8.1 Hz, 1H, Ala NH), 5.34 (dd, J = 8.9, 5.9 Hz, 1H, β-Tyr CH), 5.60 (dd, J = 9.7, 6.6 Hz, 1H, Trp CH), 6.88 (d, J = 8 Hz, 1H, β-Tyr NH), 6.80 (s, 1H, Trp H_{Ar}), 7.07–7.11 (m, 4H, Ar, Trp H_{Ar}), 7.20 (d, J = 7.9 Hz, 2H, Ar), 7.29 (d, J = 8.1 Hz, 1H, Trp H_{Ar}), 7.56 (d, J = 7.9 Hz, 1H, Trp H_{Ar}), 8.10 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), 17.0 (Ala CH_3), 18.3 ($C(CH_3)_3$), 23.0 (CH_2), 25.9 (C(CH_3)$_3$), 28.3 (C(CH_3)$_3$), 30.4 (NCH_3), 39.2 (CH_2Ar), 46.9 (Ala CH), 54.0 (β-Tyr CH), 56.5 (Trp CH), 58.7 (OMe), 64.4 (CH_2O), 80.7 ($C(CH_3)_3$), 83.4 (*C*HOCH_3), 110.4 (quat. Trp), 111.1, 118.5, 119.4, 122.0, 122.3, 127.20 (2C, Ar), 127.25 (quat. Trp), 129.3 (2C, Ar), 135.7, 136.1 (quat. Trp), 138.7, 156.4 (Boc), 169.2, 171.0, 174.6; HMRS (ESI): *m/z*: calcd for $C_{38}H_{56}N_4O_8Si$ [M+Na]$^+$: 747.37596; found: 747.37579.



21i

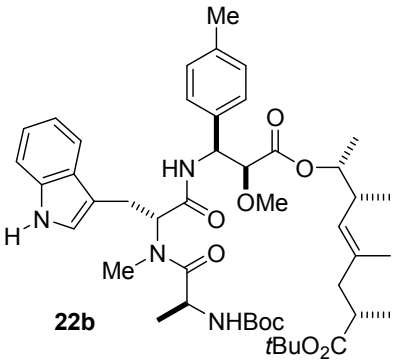
Tripeptide acid 21i (CN). To a solution of methyl ester **20i** (63.8 mg, 0.105 mmol) in THF (0.3 mL) were added water (0.4 mL), methanol (0.3 mL) and K_2CO_3 (29 mg, 0.21 mmol, 2 equiv). The initial biphasic mixture became homogeneous with progressing saponification. After being stirred overnight at room temperature until complete conversion (controlled by TLC), the mixture was diluted with water (5 mL) and ethyl acetate (8 mL). It was carefully acidified with 1M $NaHSO_4$ to pH ~ 2 before the layers were separated and the aqueous phase extracted once with ethyl acetate (8

mL). The combined organic layers were washed with water, saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21i** as a colorless foam. R_f (CH_2Cl_2/MeOH/AcOH, 10:1:0.1) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.39 (s, 9H, *t*-Bu), 2.92 (s, 3H, NCH_3), 3.17 (dd, *J* = 15.4, 10.1 Hz, 1H, CH_2), 3.28–3.33 (m, 1H, CH_2), 3.33 (s, 3H, OCH_3), 3.96 (d, *J* = 6.1 Hz, 1H, C*H*OCH_3), 4.42–4.49 (m, 1H, Ala CH), 5.36 (app t, 1H, β-Tyr CH), 5.43 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.58 (app t, 1H, Trp CH), 6.89 (s, 1H, Trp H_{Ar}), 7.06 (app t, 1H, Trp H_{Ar}), 7.12–7.17 (m, 2H, β-Tyr NH, Trp H_{Ar}), 7.291 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.37 (d, *J* = 8.1 Hz, 2H, Ar), 7.50 (d, *J* = 8.1 Hz, 2H, Ar), 7.53 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 8.34 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0 (Ala CH_3), 23.1 (CH_2), 28.3 (C(*C*H_3)$_3$), 30.6 (NCH_3), 46.9 (Ala CH), 54.1 (OMe), 56.7 (β-Tyr CH), 58.8 (Trp CH), 80.8 (*C*(CH_3)$_3$), 82.6 (*C*HOCH_3), 110.3 (quat. Trp), 111.2, 111.6 (quat.), 118.4, 118.6 (quat.), 119.5, 122.1, 122.3, 127.1 (quat. Trp), 128.2 (2C, Ar), 132.2 (2C, Ar), 136.1 (quat. Trp), 143.3, 156.3 (Boc), 169.5, 170.8, 174.7; HMRS (ESI): *m/z*: calcd for $C_{31}H_{37}N_5O_7$ [*M*+Na]$^+$: 614.25852; found: 614.25821.

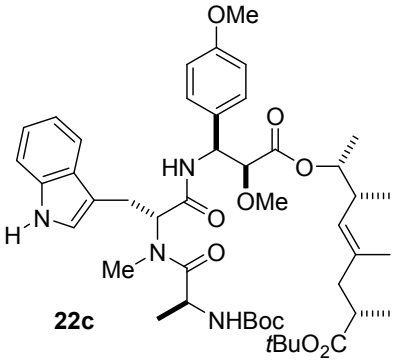


21k

Tripeptide acid 21k (Ph). To a solution of methyl ester **20k** (83.3 mg, 0.127 mmol) in THF (0.4 mL) were added water (0.6 mL), methanol (0.3 mL) and NaOH (10 mg, 0.25 mmol, 2 equiv). The initial biphasic mixture became homogeneous with progressing saponification. After being stirred for 2 h at room temperature until complete conversion (controlled by TLC), the mixture was diluted with water (5 mL) and ethyl acetate (8 mL). It was carefully acidified with 1M $NaHSO_4$ to pH ~ 2 before the layers were separated and the aqueous phase extracted once with ethyl acetate (8 mL). The combined organic layers were washed with water, saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the crude acid **21k** as a colorless foam. R_f (EtOAc/AcOH, 100:1) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 7.1 Hz, 3H, Ala CH_3), 1.41 (s, 9H, *t*-Bu), 2.92 (s, 3H, NCH_3), 3.21–3.35 (m, 2H, CH_2), 3.39 (s, 3H, OCH_3), 4.09 (d, *J* = 5.8 Hz, 1H, C*H*OCH_3), 4.42–4.49 (m, 1H, Ala CH), 5.42–5.47 (m, 2H, β-Tyr CH, Ala NH), 5.63 (dd, *J* = 9.4, 6.8 Hz, 1H, Trp CH), 6.90 (s, 1H, Trp H_{Ar}), 7.06–7.15 (m, 3H, Trp H_{Ar}, β-Tyr NH), 7.26–7.42 (m, 6H), 7.48–7.57 (m, 5H), 8.25 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0 (Ala CH_3), 23.0 (CH_2), 28.3 (C(*C*H_3)$_3$), 30.5 (NCH_3), 46.9 (Ala CH), 54.0 (β-Tyr CH), 56.6 (Trp CH), 58.8 (OCH_3), 80.8 (*C*(CH_3)$_3$), 83.3 (*C*HOCH_3), 110.4 (quat. Trp), 111.1, 118.4, 119.4, 122.0, 122.3, 127.0 (2C, Ar), 127.22 (2C, Ar), 127.26 (quat. Trp), 127.31 (Ar), 127.8 (2C, Ar), 128.7 (2C, Ar), 136.1 (quat. Trp), 136.9, 140.6, 140.7, 156.4 (Boc), 169.34, 171.0, 174.7;

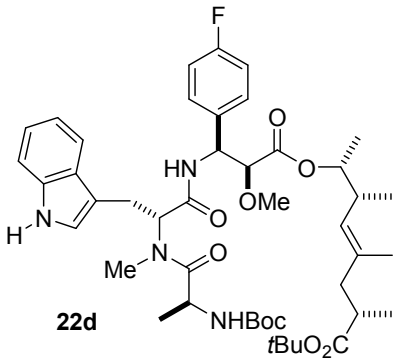


Depsipeptide 22b (Me). The crude acid **21b**, resulting from the hydrolysis of ester **20b** (57 mg, 0.096 mmol), and alcohol **7** (23 mg, 0.146 mmol) were dissolved in THF (6 mL) and Ph_3P (75 mg, 0.288 mmol) was added at 0 °C. This was followed by the dropwise addition of DEAD (0.131 mL, 0.288 mmol, 40% in toluene). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give ester **22b** (46 mg, 67% over two steps) as a colorless foam. R_f (petroleum ether/EtOAc, 2:1) 0.23; $[\alpha]^{20}_D$ = +3.3 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.6 Hz, 3H, CH_3), 0.88 (d, *J* = 6.3 Hz, 3H, CH_3), 0.92 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.02 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.40 (s, 9H, C$(CH_3)_3$), 1.41 (s, 9H, C$(CH_3)_3$), 1.57 (s, 3H, 4-CH_3), 1.93 (dd, *J* = 13.9, 7.8 Hz, 1H, CH_2), 2.27 (s, 3H, ArCH_3), 2.34 (dd, *J* = 13.6, 6.8 Hz, 1H, CH_2), 2.40–2.50 (m, 2H, 2-H, 6-H), 2.95 (s, 3H, NCH_3), 3.20–3.28 (m, 1H, Trp CH_2), 3.34 (dd, *J* = 15.9, 6.3 Hz, 1H, Trp CH_2), 3.37 (s, 3H, OCH_3), 4.06 (d, *J* = 4.3 Hz, 1H, CHOCH_3), 4.48–4.60 (m, 2H, Ala CH, 7-H), 4.86 (d, *J* = 9.4 Hz, 1H, 5-H), 5.37 (dd, *J* = 8.6, 4.6 Hz, 1H, β-Tyr CH), 5.44 (d, *J* = 7.3 Hz, 1H, Ala NH), 5.52 (dd, *J* = 10.1, 6.3 Hz, 1H, Trp CH), 6.91 (s, 1H, Trp H_{Ar}), 7.04 (d, *J* = 8.1 Hz, 2H, β-Tyr H_{Ar}), 7.06–7.12 (m, 2H, Trp H_{Ar}, β-Tyr NH), 7.12–7.19 (m, 3H, Trp H_{Ar}, β-Tyr H_{Ar}), 7.29 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.58 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 8.03 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (4-CH_3), 16.6 (2-CH_3), 17.1 (6-CH_3), 17.6 (7-CH_3), 18.1 (Ala CH_3), 21.1 (ArCH_3), 23.4 (Trp CH_2), 28.1 (C(*C*H)$_3$), 28.3 (C(*C*H)$_3$), 30.8 (NCH_3), 37.6 (C-6), 38.6 (C-2), 43.4 (CH_2), 46.7 (Ala CH), 54.0 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH_3), 75.9 (C-7), 79.5 (*C*(CH)$_3$), 79.9 (*C*(CH)$_3$), 82.1 (*C*HOCH$_3$), 110.9 (Trp C_{ar}), 111.1 (Trp C_{ar}), 118.5 (Trp C_{ar}), 119.5 (Trp C_{ar}), 122.1 (Trp C_{ar}), 127.3 (Trp C_{ar}), 127.9 (β-Tyr C_{ar}), 127.9 (C-5), 129.0 (β-Tyr C_{ar}), 133.7 (C-4, β-Tyr C_{ar}), 136.1 (Trp C_{ar}), 137.6 (β-Tyr Car), 155.1 (CO), 169.3 (CO), 174.3 (CO), 175.8 (CO); HRMS (ESI): *m/z*: calcd for $C_{46}H_{66}N_4O_9$ $[M+Na]^+$: 841.47220; found: 841.47301.



Depsipeptide 22c (OMe). The crude acid **21c**, resulting from the hydrolysis of ester **20c** (135 mg, 0.221 mmol) and alcohol **7** (52 mg, 0.336 mmol) were dissolved in THF (12 mL) and Ph_3P (174 mg, 0.663 mmol) was added at 0 °C. This was followed by the dropwise addition of DEAD (0.302 mL, 0.663 mmol, 40% in toluene). The cooling bath was removed and the mixture stirred overnight

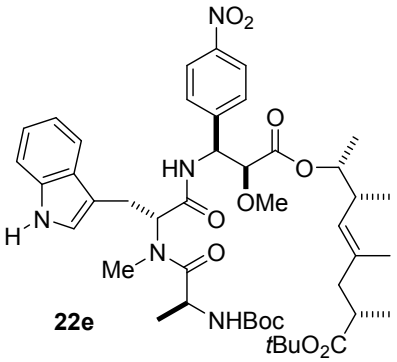
at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give ester **22c** (99 mg, 61% over two steps) as a colorless foam. R_f (petroleum ether/EtOAc, 3:2) 0.19; $[\alpha]^{20}_D$ = +14.8 (*c* 1.00, CH_2Cl_2); ^{1}H MR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.6 Hz, 3H, 6-CH_3), 0.88 (d, *J* = 6.1 Hz, 3H, 7-CH_3), 0.91 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.01 (d, *J* = 6.9 Hz, 3H, 2-CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.57 (s, 3H, 4-CH_3), 1.93 (dd, *J* = 13.7, 7.6 Hz, 1H, CH_2), 2.34 (dd, *J* = 13.7, 6.9 Hz, 1H, CH_2), 2.40–2.51 (m, 2H, 2-H, 6-H), 2.95 (s, 3H, NCH_3), 3.23 (dd, *J* = 15.6, 10.1 Hz, 1H, Trp CH_2), 3.34 (dd, *J* = 16.0, 6.1 Hz, 1H, Trp CH_2), 3.39 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.05 (d, *J* = 4.3 Hz, 1H, C*H*OCH_3), 4.47–4.54 (m, 1H, Ala CH), 4.53–4.61 (m, 1H, 7-H), 4.86 (d, *J* = 9.7 Hz, 1H, 5-H), 5.35 (dd, *J* = 8.4, 4.6 Hz, 1H, β-Tyr CH), 5.42 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.52 (dd, *J* = 9.7, 6.6 Hz, 1H, Trp CH), 6.75 (d, *J* = 8.7 Hz, 2H, β-Tyr H_{ar}), 6.89 (s, 1H, Trp H_{ar}), 7.03–7.08 (m, 1H, β-Tyr NH), 7.07–7.11 (m, 1H, Trp H_{ar}), 7.15 (t, *J* = 7.4 Hz, 1H, Trp H_{ar}), 7.20 (d, *J* = 8.4 Hz, 2H, β-Tyr H_{ar}), 7.29 (d, *J* = 7.9 Hz, 1H, Trp H_{ar}), 7.57 (d, *J* = 7.6 Hz, 1H, Trp H_{ar}), 8.19 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (4-CH_3), 16.6 (2-CH_3), 17.1 (6-CH_3), 17.6 (7-CH_3), 18.1 (Ala CH_3), 23.4 (Trp CH_2), 28.0 ($C(CH)_3$), 28.3 ($C(CH)_3$), 30.8 (NCH_3), 37.6 (C-6), 38.6 (C-2), 43.4 (CH_2), 46.7 (Ala CH), 53.7 (β-Tyr CH), 55.2 (OCH_3), 56.7 (Trp CH), 59.2 (OCH_3), 75.8 (C-7), 79.5 ($C(CH)_3$), 79.8 ($C(CH)_3$), 82.0 ($CHOCH_3$), 110.7 (Trp C_{ar}), 111.1 (Trp C_{ar}), 113.7 (β-Tyr C_{ar}), 118.5 (Trp C_{ar}), 119.4 (Trp C_{ar}), 122.0 (Trp C_{ar}), 122.1 (Trp C_{ar}), 127.2 (Trp C_{ar}), 127.9 (C-5), 128.9 (β-Tyr C_{ar}), 129.2 (β-Tyr C_{ar}), 133.7 (C-4), 136.1 (Trp C_{ar}), 155.1 (CO), 159.2 (β-Tyr C_{ar}), 169.2 (CO), 169.2 (CO), 174.3 (CO), 175.8 (CO); HRMS (ESI): *m/z*: calcd for $C_{46}H_{66}N_4O_{10}$ $[M+Na]^+$: 857.46712; found: 857.46651.



22d

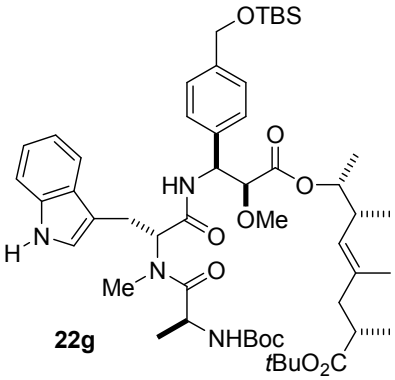
Depsipeptide 22d (F). The crude acid **21d**, resulting from the hydrolysis of ester **20d** (57 mg, 0.095 mmol) and alcohol **7** (22 mg, 0.144 mmol) were dissolved in THF (6 mL) and Ph_3P (75 mg, 0.285 mmol) was added at 0 °C. This was followed by the dropwise addition of DEAD (0.130 mL, 0.285 mmol, 40% in toluene). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give ester **22d** (44 mg, 64% over two steps) as a colorless foam. R_f (petroleum ether/EtOAc, 2:1) 0.29; $[\alpha]^{20}_D$ = +10.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.6 Hz, 3H, 6-CH_3), 0.88 (d, *J* = 6.4 Hz, 3H, 7-CH_3), 0.93 (d, *J* = 6.6 Hz, 3H, Ala CH_3), 1.02 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.57 (s, 3H, 4-CH_3), 1.93 (dd, *J* = 14.0, 7.6 Hz, 1H, CH_2), 2.34 (dd, *J* = 13.7, 6.9 Hz, 1H, CH_2), 2.39–2.50 (m, 2H, 2-H, 6-H), 2.96 (s, 3H, NCH_3), 3.22 (dd, *J* = 15.5, 9.7 Hz, 1H, Trp CH_2), 3.30–3.39 (m, 1H, Trp CH_2), 3.40 (s, 3H, OCH_3), 4.05 (d, *J* = 4.3 Hz, 1H, C*H*OCH_3), 4.45–4.60 (m, 2H, Ala CH, 7-H), 4.85 (d, *J* = 9.4 Hz, 1H, 5-H), 5.34–5.41 (m, 2H, β-Tyr CH, Ala NH), 5.52 (dd, *J* = 9.5, 6.5 Hz, 1H, Trp CH), 6.87–6.94 (s, 3H, Trp H_{ar}, β-Tyr H_{ar}), 7.05–7.13 (m, 2H, Trp H_{ar}, β-Tyr NH), 7.16 (t, *J* = 7.6 Hz, 1H, Trp H_{ar}), 7.21–7.29 (m, 2H, β-Tyr H_{ar}), 7.31 (d, *J* = 8.1 Hz, 1H, Trp H_{ar}), 7.58 (d, *J* = 7.9 Hz, 1H, Trp H_{ar}), 8.07 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (4-CH_3), 16.6 (2-CH_3), 17.1 (6-CH_3), 17.6 (7-CH_3), 18.0 (Ala CH_3), 23.4 (Trp CH_2), 28.0

(C(CH_3)$_3$), 28.3 (C(CH_3)$_3$), 30.8 (NCH_3), 37.6 (C-6), 38.6 (C-2), 43.4 (CH_2), 46.7 (Ala CH), 53.6 (β-Tyr CH), 56.7 (Trp CH), 59.2 (OCH_3), 76.0 (C-7), 79.6 ($C(CH_3)_3$), 79.9 ($C(CH_3)_3$), 81.8 ($CHOCH_3$), 110.8 (Trp C_{ar}), 111.1 (Trp C_{ar}), 115.1 (d, J = 22.0 Hz, β-Tyr C_{ar}), 118.5 (Trp C_{ar}), 119.5 (Trp C_{ar}), 122.1 (Trp C_{ar}), 122.1 (Trp C_{ar}), 127.2 (Trp C_{ar}), 127.8 (C-5), 129.9 (d, J = 8.1 Hz, β-Tyr C_{ar}), 132.7 (d, J = 3.7 Hz, β-Tyr C_{ar}), 133.8 (C-4), 136.1 (Trp C_{ar}), 155.2 (CO), 162.4 (d, J = 146.6 Hz, β-Tyr Car), 169.1 (CO), 169.3 (CO), 174.4 (CO), 175.8 (CO); HRMS (ESI): *m/z*: calcd for $C_{45}H_{63}FN_4O_9$ [M+Na]$^+$: 845.44713; found: 845.44760.



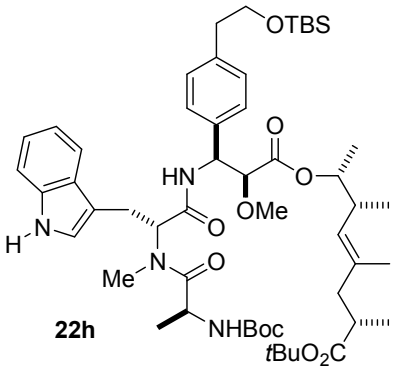
22e

Depsipeptide 22e (NO_2). The crude acid **21e** (52 mg, 0.0851 mmol) and alcohol **7** (32.8 mg, 0.128 mmol, 1.5 equiv) were dissolved in THF (1 mL) and Ph_3P (40 mg, 0.152 mmol, 1.8 equiv) was added at 0 °C. This was followed by the dropwise addition of DIAD (0.030 mL, 0.152 mmol, 1.8 equiv). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1 to 1:1) to give ester **22e** (62 mg, 86%) as a colorless foam. R_f (petroleum ether/EtOAc, 1:1) 0.30; $[\alpha]^{20}_D$ = –4.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, J = 6.6 Hz, 3H, CH_3), 0.91 (d, J = 6.1 Hz, 3H, CH_3), 0.96 (d, J = 6.8 Hz, 3H, Ala CH_3), 1.01 (d, J = 6.8 Hz, 3H, CH_3), 1.40 (s, 9H, *t*-Bu), 1.41 (s, 9H, *t*-Bu), 1.56 (s, 3H, CH_3), 1.92 (dd, J = 13.9, 7.6 Hz, 1H, CH_2), 2.33 (dd, J = 13.9, 6.8 Hz, 1H, CH_2), 2.40–2.51 (m, 2H, 2 CH), 2.97 (s, 3H, NCH_3), 3.17 (dd, J = 15.4, 9.6 Hz, 1H, CH_2), 3.37 (dd, J = 15.4, 7.1 Hz, 1H, CH_2), 3.40 (s, 3H, OCH_3), 4.06 (d, J = 4.5 Hz, 1H, C*H*OCH_3), 4.46–4.61 (m, 2H, Ala CH, CO_2CH), 4.84 (d, J = 9.9 Hz, 1H, =CH), 5.34 (d, J = 7.3 Hz, 1H, Ala NH), 5.43 (dd, J = 8.3, 4.5 Hz, 1H, β-Tyr CH), 5.52 (dd, J = 9.6, 7.1 Hz, 1H, Trp CH), 6.88 (s, 1H, Trp H_{Ar}), 7.07 (ddd, J = 7.8, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.15 (ddd, J = 8.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.21 (d, J = 8.3 Hz, 1H, β-Tyr NH), 7.30 (d, J = 8.1 Hz, 1H, Trp H_{Ar}), 7.39 (d, J = 8.6 Hz, 2H, Ar), 7.56 (d, J = 7.8 Hz, 1H, Trp H_{Ar}), 8.04 (d, J = 8.6 Hz, 2H, Ar), 8.25 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 16.6, 17.1, 17.6, 17.9, 23.5 (CH_2), 28.0 (C(CH_3)$_3$), 28.3 (C(CH_3)$_3$), 30.9 (NMe), 37.5, 38.6, 43.4 (CH_2), 46.7 (Ala CH), 53.8 (β-Tyr CH), 56.8 (Trp CH), 59.3 (OCH_3), 76.4 (CO_2CH), 79.6 ($C(CH_3)_3$), 79.9 ($C(CH_3)_3$), 81.4 ($CHOCH_3$), 110.5 (quat. Trp), 111.1, 118.4, 119.5, 122.1, 122.2, 123.3 (2C, Ar), 127.1 (quat. Trp), 127.5 (=CH), 129.1 (2C, Ar), 134.0 (=C<), 136.1 (quat. Trp), 144.3, 147.4, 155.2 (Boc), 168.6, 169.5, 174.5, 175.7; HMRS (ESI): *m/z*: calcd for $C_{45}H_{63}N_5O_{11}$ [M+Na]$^+$: 872.44163; found: 872.44212.



22g

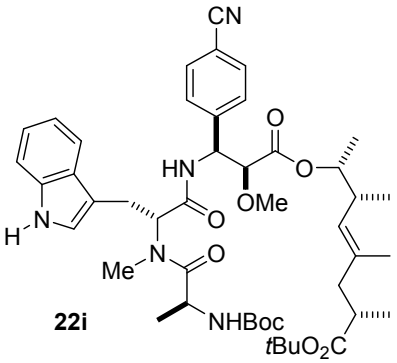
Depsipeptide 22g (CH_2OTBS). The crude acid **21g** (60.2 mg, 0.0847 mmol) and alcohol **7** (37.7 mg, 0.147 mmol, 1.7 equiv) were dissolved in THF (1 mL) and Ph_3P (40 mg, 0.152 mmol, 1.8 equiv) was added at 0 °C. This was followed by the dropwise addition of DEAD (0.070 mL of 40% in toluene, 1.8 equiv). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/acetone, 3:1 to 2:1) to give ester **22g** (64.5 mg, contaminated with diethyl hydrazodicarboxylate (9% mass) byproduct = 58.7 mg, 73%) as a white foam. $[\alpha]^{20}_D$ = +3.4 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (2s, 6H, $SiCH_3$), 0.77 (d, *J* = 6.8 Hz, 3H, CH_3), 0.86 (d, *J* = 6.3 Hz, 3H, CH_3), 0.92 (s, 9H, *t*-BuSi), 0.96 (d, *J* = 6.6 Hz, 3H, Ala CH_3), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3), 1.40 (s, 18H, *t*-Bu), 1.56 (s, 3H, CH_3), 1.92 (dd, *J* = 13.9, 7.6 Hz, 1H, CH_2), 2.33 (dd, *J* = 13.7, 6.8 Hz, 1H, CH_2), 2.40–2.50 (m, 2H, 2 CH), 2.98 (s, 3H, NCH_3), 3.17 (dd, *J* = 15.4, 9.3 Hz, 1H, CH_2), 3.34 (dd, *J* = 15.4, 6.6 Hz, 1H, CH_2), 3.40 (s, 3H, OCH_3), 4.05 (d, *J* = 4.6 Hz, 1H, C*H*OCH_3), 4.49–4.58 (m, 2H, Ala CH, CO_2CH), 4.66 (s, 2H, $ArCH_2$), 4.85 (d, *J* = 9.9 Hz, 1H, =CH), 5.38 (dd, *J* = 8.7, 4.6 Hz, 1H, β-Tyr CH), 5.44–5.49 (m, 2H, Ala NH, Trp CH), 6.77 (s, 1H, Trp H_{Ar}), 7.02 (d, 1H, *J* = 8.7 Hz, β-Tyr NH), 7.09 (ddd, *J* = 7.8, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.13–7.23 (m, 5H, Trp H_{Ar}, Ar), 7.28 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.57 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 8.16 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.30, –5.28, 16.4, 16.6, 17.1, 17.6, 18.2, 18.4, 23.6 (CH_2), 25.9 ($SiC(CH_3)_3$), 28.0 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 30.8 (NCH_3), 37.6, 38.6, 43.4 (CH_2), 46.7 (Ala CH), 53.9 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH_3), 64.8 (CH_2O), 75.9 (CO_2CH), 79.5 ($C(CH_3)_3$), 79.8 ($C(CH_3)_3$), 81.9 ($CHOCH_3$), 110.4 (quat. Trp), 111.1, 118.4, 119.4, 122.0, 122.3, 126.2, 127.1, 127.91, 127.97, 133.7 (=C<), 135.6, 136.0 (quat. Trp), 140.9, 155.1 (Boc), 169.1, 169.3, 174.1, 175.8; HMRS (ESI): *m/z*: calcd for $C_{52}H_{80}N_4O_{10}Si$ $[M+Na]^+$: 971.55359; found: 971.55362.



22h

Depsipeptide 22h (CH_2CH_2OTBS). The crude acid **21h** (59.0 mg, 0.0814 mmol) and alcohol **7** (31.4 mg, 0.123 mmol, 1.5 equiv) were dissolved in THF (1 mL) and Ph_3P (42.7 mg, 0.163 mmol, 2 equiv) was added at 0 °C. This was followed by the dropwise addition of DEAD (0.075 mL of 40% in toluene, 0.164 mmol, 2 equiv). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by

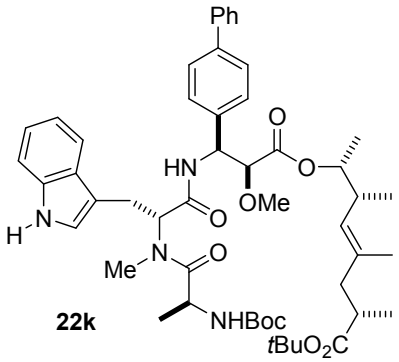
flash chromatography (petroleum ether/EtOAc, 1:2) to give ester **22h** (51.8 mg, 66%) as a colorless foam. In this case separation from the diethyl hydrazodicarboxylate byproduct is difficult and requires separation at high R_f's. $[\alpha]^{20}_D$ = +1.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $SiCH_3$), 0.77 (d, *J* = 6.6 Hz, 3H, CH_3), 0.87 (s, 12H, CH_3, *t*BuSi), 0.97 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 1.01 (d, *J* = 6.9 Hz, 3H, CH_3), 1.41 (s, 18H, *t*Bu), 1.57 (s, 3H, CH_3), 1.92 (dd, *J* = 13.7, 7.9 Hz, 1H, CH_2), 2.33 (dd, *J* = 13.7, 6.9 Hz, 1H, CH_2), 2.40–2.50 (m, 2H, CH+CH), 2.75 (t, *J* = 6.9 Hz, 2H, $ArCH_2$), 2.99 (s, 3H, NCH_3), 3.17 (dd, *J* = 15.3, 9.3 Hz, 1H, CH_2), 3.34 (dd, *J* = 15.3, 6.6 Hz, 1H, CH_2), 3.39 (s, 3H, OCH_3), 3.79 (t, *J* = 6.9 Hz, 2H, CH_2O), 4.03 (d, *J* = 4.6 Hz, 1H, C*H*OCH_3), 4.50–4.59 (m, 2H, Ala CH, CO_2CH), 4.85 (d, *J* = 9.7 Hz, 1H, =CH), 5.36 (dd, *J* = 8.7, 4.6 Hz, 1H, β-Tyr CH), 5.44–5.48 (m, 2H, Ala NH, Trp CH), 6.79 (s, 1H, Trp H_{Ar}), 6.98 (d, 1H, *J* = 8.7 Hz, β-Tyr NH), 7.05–7.16 (m, 6H, Ar, Trp H_{Ar}), 7.27 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.57 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 8.15 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.36, –5.33, 16.4, 16.6, 17.1, 17.6, 18.2, 18.3, 23.6 (CH_2), 25.9 ($SiC(CH_3)_3$), 28.0 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 30.8 (NCH_3), 37.6, 38.6, 39.2 ($ArCH_2$), 43.4 (CH_2), 46.7 (Ala CH), 53.9 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH_3), 64.5 (CH_2O), 75.8 (CO_2CH), 79.5 ($C(CH_3)_3$), 79.8 ($C(CH_3)_3$), 82.0 ($CHOCH_3$), 110.3 (quat. Trp), 111.1, 118.4, 119.3, 121.9, 122.3, 127.1 (quat. Trp), 127.9 (3C, Ar, =CH), 129.0 (2C, Ar), 133.7 (=C<), 134.7, 136.1 (quat. Trp), 138.6, 155.1 (Boc), 169.1, 169.2, 174.1, 175.8; HMRS (ESI): *m/z*: calcd for $C_{53}H_{82}N_4O_{10}Si$ $[M+Na]^+$: 985.56924; found: 985.56858.



22i

Depsipeptide 22i (CN). The crude acid **21i** (54.9 mg, 0.0927 mmol) and alcohol **7** (35.7 mg, 0.139 mmol, 1.5 equiv) were dissolved in THF (0.93 mL) and Ph_3P (41.3 mg, 0.158 mmol, 1.7 equiv) was added at 0 °C. This was followed by the dropwise addition of DIAD (0.031 mL, 0.158 mmol, 1.7 equiv). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 1:1 to 1:2) to give ester **22i** (60.1 mg, 78%) as a colorless foam. R_f (petroleum ether/EtOAc, 1:2) 0.58; $[\alpha]^{20}_D$ = –5.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.6 Hz, 3H, CH_3), 0.89 (d, *J* = 6.3 Hz, 3H, CH_3), 0.95 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.02 (d, *J* = 6.8 Hz, 3H, CH_3), 1.40 (s, 9H, *t*-Bu), 1.41 (s, 9H, *t*-Bu), 1.57 (s, 3H, CH_3), 1.93 (dd, *J* = 13.7, 7.7 Hz, 1H, CH_2), 2.33 (dd, *J* = 13.7, 6.8 Hz, 1H, CH_2), 2.40–2.50 (m, 2H, 2 CH), 2.97 (s, 3H, NCH_3), 3.19 (dd, *J* = 15.7, 9.6 Hz, 1H, CH_2), 3.37 (dd, *J* = 15.7, 6.3 Hz, 1H, CH_2), 3.40 (s, 3H, OCH_3), 4.03 (d, *J* = 4.8 Hz, 1H, C*H*OCH_3), 4.47–4.60 (m, 2H, Ala CH, CO_2CH), 4.85 (d, *J* = 9.4 Hz, 1H, =CH), 5.34 (d, *J* = 7.6 Hz, 1H, Ala NH), 5.39 (dd, *J* = 8.3, 4.8 Hz, 1H, β-Tyr CH), 5.51 (dd, *J* = 8.9, 6.8 Hz, 1H, Trp CH), 6.90 (s, 1H, Trp H_{Ar}), 7.09 (ddd, *J* = 7.8, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.15–7.20 (m, 2H, Trp H_{Ar}, NH), 7.32 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.36 (d, *J* = 8.1 Hz, 2H, Ar), 7.51 (d, *J* = 8.1 Hz, 2H, Ar), 7.57 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 8.05 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 16.7, 17.1, 17.6, 18.0, 23.5 (CH_2), 28.1 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 30.9 (NCH_3), 37.5, 38.6, 43.4 (CH_2), 46.7 (Ala CH), 54.0 (β-Tyr CH), 56.8 (Trp CH), 59.3 (OCH_3), 76.4 (CO_2CH), 79.7 ($C(CH_3)_3$), 79.9 ($C(CH_3)_3$), 81.5 ($CHOCH_3$), 110.7 (quat. Trp), 111.1, 111.8, 118.5, 118.6, 119.6, 122.1, 122.2, 127.1 (quat. Trp), 127.6 (=CH), 129.0, 132.0, 134.0 (=C<), 136.1

(quat. Trp), 142.3, 155.2 (Boc), 168.7, 169.5, 174.5, 175.7; HMRS (ESI): *m/z*: calcd for $C_{46}H_{63}N_5O_9$ [*M*+Na]$^+$: 852.45180; found: 852.45123.



22k

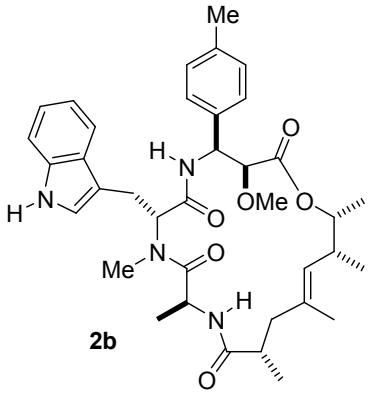
Depsipeptide 22k (Ph). The crude acid **21k** (81.5 mg, 0.127 mmol) and alcohol **7** (39.2 mg, 0.152 mmol, 1.2 equiv) were dissolved in THF (1.3 mL) and Ph_3P (50 mg, 0.190 mmol, 1.5 equiv) was added at 0 °C. This was followed by the dropwise addition of DIAD (0.037 mL, 0.190 mmol, 1.5 equiv). The cooling bath was removed and the mixture stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1 to 1:1 to 0:1) to give ester **22k** (62.6 mg, 56%) as a colorless foam. $[\alpha]^{20}_D$ = –10.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.6 Hz, 3H, CH_3), 0.89 (d, *J* = 6.1 Hz, 3H, CH_3), 0.93 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3), 1.41 (s, 18H, *t*-Bu), 1.56 (s, 3H, CH_3), 1.93 (dd, *J* = 13.9, 7.6 Hz, 1H, CH_2), 2.34 (dd, *J* = 13.9, 6.8 Hz, 1H, CH_2), 2.40–2.51 (m, 2H, 2 CH), 2.97 (s, 3H, NCH_3), 3.24 (dd, *J* = 15.7, 10.1 Hz, 1H, CH_2), 3.37 (dd, *J* = 15.7, 6.6 Hz, 1H, CH_2), 3.43 (s, 3H, OCH_3), 4.10 (d, *J* = 4.3 Hz, 1H, C*H*OCH_3), 4.50–4.62 (m, 2H, Ala CH, CO_2CH), 4.86 (d, *J* = 9.6 Hz, 1H, =CH), 5.56 (m, 2H, Ala NH, β-Tyr CH), 5.56 (dd, *J* = 9.9, 6.6 Hz, 1H, Trp CH), 6.90 (s, 1H, Trp H_{Ar}), 7.08–7.20 (m, 3H, Trp H_{Ar}, β-Tyr NH), 7.29–7.35 (m, 4H), 7.41 (t, 2H), 7.46 (d, 2H, *J* = 8.1 Hz), 7.52 (d, 2H, *J* = 7.1 Hz), 7.59 (d, 1H, *J* = 7.6 Hz), 8.18 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 16.6, 17.1, 17.6, 18.1, 23.4 (CH_2), 28.0 (C(*C*H_3)$_3$), 28.3 (C(*C*H_3)$_3$), 30.8 (NCH_3), 37.6, 38.6, 43.4 (CH_2), 46.7 (Ala CH), 53.9 (β-Tyr CH), 56.8 (Trp CH), 59.2 (OCH_3), 76.0 (CO_2*C*H), 79.5 (*C*$(CH_3)_3$), 79.8 (*C*$(CH_3)_3$), 82.0 (*C*HOCH_3), 110.7 (quat. Trp), 111.1, 118.5, 119.4, 122.05, 122.14, 127.00, 127.03, 127.19, 127.24, 127.8 (=CH), 128.4, 128.7, 133.7 (=C<), 135.8, 136.1 (quat. Trp), 140.72, 140.76, 155.1 (Boc), 169.2, 169.3, 174.3, 175.8. HMRS (ESI): *m/z*: calcd for $C_{51}H_{68}N_4O_9$ [*M*+Na]$^+$: 903.48785; found: 903.48732.

Chondramide A analogues

Deprotection. Double Boc-deprotection was carried out in 1:10 v/v solution of TFA/CH_2Cl_2 at room temperature overnight at 0.03M concentration of a substrate (the progress of reaction was easily monitored by TLC in CH_2Cl_2/MeOH/NH_3 10:1:0.1 and NMR, in each case complete and clean conversion was achieved after ~20 h). The solvent was removed in vacuo. For azeotropic removal of TFA, the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time.

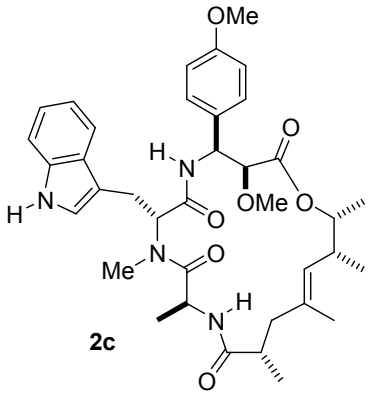
Macrolactam formation. In most cases macrolactamization was carried out at 0.0025M concentration instead of 0.001M without loss of efficacy. The crude product from the deprotection step was dissolved in DMF and *i*Pr_2NEt (5 equiv), HOBt (1.5 equiv), and TBTU (1.5 equiv) were added. The solution was stirred at room temperature for 20 h and then diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (3 times) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution, water, saturated $NaHCO_3$ solution, water, and

saturated NaCl solution. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography.

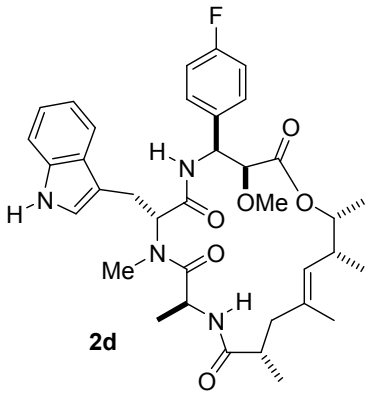


2b

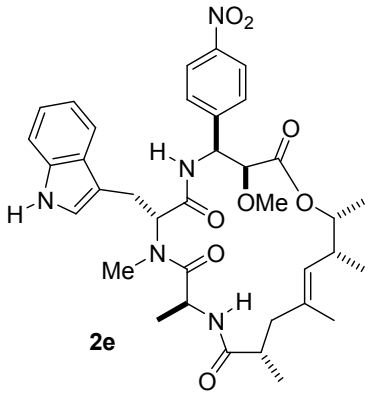
Chondramide 2b (Me). To a stirred solution of compound **22b** (42 mg, 0.051 mmol) in CH_2Cl_2 (1 mL) was added TFA (38 µL, 0.51 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo. For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in DMF (50 mL) and *i*Pr_2NEt (34 µL, 0.204 mmol), HOBt (24.0 mg, 0.179 mmol) and TBTU (56.0 mg, 0.179 mmol) were added. The solution was stirred at room temperature for 20 h and then diluted with water (25 mL) and EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (25 mL), water (25 mL), saturated $NaHCO_3$ solution (25 mL), water (2 × 25 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/acetone, 2:1) of the residue to give depsipeptide **2b** (11 mg, 33% over two steps) as a colorless foam. R_f (petroleum ether/acetone, 2:1) 0.18; $[\alpha]^{20}_D$ = +23.9 (*c* 0.83, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.81 (d, *J* = 7.1 Hz, 3H, Ala CH_3), 0.86 (d, *J* = 6.3 Hz, 3H, 7-CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, 6-CH_3), 1.08 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.69 (s, 3H, 4-CH_3), 1.98–2.06 (m, 1H, CH_2), 2.15–2.27 (m, 1H, CH_2), 2.32 (s, 3H, ArCH_3), 2.45–2.55 (m, 1H, 6-H), 2.60–2.71 (m, 1H, 2-H), 3.01 (d, J = 8.1 Hz, 2H, Trp CH_2), 3.08 (s, 3H, NCH_3), 3.13 (s, 3H, OCH_3), 3.88 (d, *J* = 9.9 Hz, 1H, C*H*OCH_3), 4.48–4.57 (m, 1H, 7-H), 4.74–4.81 (m, 1H, Ala CH), 4.82–4.85 (m, 1H, 5-H), 5.06 (d, *J* = 9.9 Hz, 1H, β-Tyr CH), 5.52 (dd, *J* = 8.0, 8.0 Hz, 1H, Trp CH), 6.83 (s, 1H, Trp H_{ar}), 6.97 (t, *J* = 7.1, 1H, Trp H_{ar}), 7.00–7.08 (m, 5H, β-Tyr H_{ar}, Trp H_{ar}), 7.25 (d, *J* = 8.1 Hz, 1H, Trp H_{ar}), 7.55 (d, *J* = 7.8 Hz, 1H, Trp H_{ar}); ^{13}C NMR (100 MHz, CD_3OD): δ = 16.0 (4-CH_3), 17.9 (6-CH_3), 18.4 (Ala CH_3), 18.9 (7-CH_3), 19.0 (2-CH_3), 21.2 (ArCH_3), 26.5 (Trp CH_2), 30.9 (NCH_3), 38.7 (C-6), 40.2 (C-2), 45.9 (Ala CH), 46.0 (CH_2), 55.9 (β-Tyr CH), 56.9 (Trp CH), 58.2 (OCH_3), 79.2 (C-7), 83.3 (*C*HOCH_3), 110.1 (Trp C_{ar}), 112.2 (Trp C_{ar}), 119.4 (Trp C_{ar}), 119.6 (Trp C_{ar}), 122.2 (Trp C_{ar}), 124.4 (Trp C_{ar}), 128.3 (β-Tyr Car), 128.5 (Trp C_{ar}), 129.0 (C-5), 129.9 (β-Tyr C_{ar}), 134.7 (C-4), 137.4 (β-Tyr C_{ar}), 137.9 (Trp C_{ar}), 138.4 (β-Tyr C_{ar}), 171.3 (CO), 173.4 (CO), 174.9 (CO), 176.9 (CO); HRMS (ESI): *m/z*: calcd for $C_{37}H_{48}N_4O_6$ $[M+Na]^+$: 667.34661; found: 667.34683.



Chondramide 2c (OMe). To a stirred solution of compound **22c** (87.0 mg, 0.104 mmol) in CH_2Cl_2 (1 mL) was added TFA (154 µL, 2.08 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo. For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in DMF (104 mL) and *i*Pr_2NEt (71 µL, 0.416 mmol), HOBt (49.0 mg, 0.364 mmol) and TBTU (114 mg, 0.364 mmol) were added. The solution was stirred at room temperature for 20 h and then diluted with water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (50 mL), water (50 mL), saturated $NaHCO_3$ solution (50 mL), water (2 × 40 mL) and saturated NaCl solution (50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 2:7) to give depsipeptide **2c** (21.3 mg, 31% over two steps) as a colorless foam. R_f (petroleum ether/EtOAc, 2:7) 0.20; $[\alpha]^{20}_D$ = +6.0 (*c* 0.40, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.83 (d, *J* = 6.9 Hz, 3H, Ala CH_3), 0.86 (d, *J* = 6.1 Hz, 3H, 7-CH_3), 0.92 (d, *J* = 6.9 Hz, 3H, 6-CH_3), 1.08 (d, *J* = 6.9 Hz, 3H, 2-CH_3), 1.69 (s, 3H, 4-CH_3), 2.04 (dd, *J* = 13.1, 2.9 Hz, 1H, CH_2), 2.23 (dd, *J* = 12.5, 12.5 Hz, 1H, CH_2), 2.46–2.58 (m, 1H, 6-H), 2.61–2.72 (m, 1H, 2-H), 2.97–3.06 (m, 2H, Trp CH_2), 3.08 (s, 3H, NCH_3), 3.13 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 (d, *J* = 9.9 Hz, 1H, C*H*OCH_3), 4.48–4.56 (m, 1H, 7-H), 4.75–4.81 (m, 1H, Ala CH), 4.81–4.85 (m, 1H, 5-H), 5.05 (d, *J* = 9.9 Hz, 1H, β-Tyr CH), 5.53 (dd, *J* = 8.0, 8.0 Hz, 1H, Trp CH), 6.77 (d, *J* = 8.7 Hz, 2H, β-Tyr H_{ar}), 6.83 (s, 1H, Trp H_{ar}), 6.95–7.01 (m, 1H, Trp H_{ar}), 7.04 (d, *J* = 8.7 Hz, 2H, β-Tyr Har), 7.05–7.08 (m, 1H, Trp H_{ar}), 7.25 (d, *J* = 8.1 Hz, 1H, Trp H_{ar}), 7.57 (d, *J* = 7.6 Hz, 1H, Trp H_{ar}); ^{13}C NMR (100 MHz, CD_3OD): δ = 16.0 (4-CH_3), 17.9 (6-CH_3), 18.4 (Ala CH_3), 18.9 (7-CH_3), 19.0 (2-CH_3), 26.5 (Trp CH_2), 30.9 (NCH_3), 38.7 (C-6), 40.2 (C-2), 45.9 (Ala CH), 46.1 (CH_2), 55.6 (β-Tyr CH), 55.7 (OCH_3), 56.9 (Trp CH), 58.2 (OCH_3), 79.2 (C-7), 83.4 (*C*HOCH_3), 110.1 (Trp C_{ar}), 112.2 (Trp C_{ar}), 114.6 (β-Tyr C_{ar}), 119.4 (Trp C_{ar}), 119.6 (Trp C_{ar}), 122.3 (Trp C_{ar}), 124.5 (Trp C_{ar}), 128.5 (Trp C_{ar}), 129.0 (C-5), 129.5 (β-Tyr C_{ar}), 132.5 (β-Tyr C_{ar}), 134.7 (C-4), 137.9 (Trp C_{ar}), 160.5 (β-Tyr C_{ar}), 171.2 (CO), 173.4 (CO), 174.9 (CO), 176.9 (CO); HRMS (ESI): m/z: calcd for $C_{37}H_{48}N_4O_7$ $[M+Na]^+$: 683.34152; found: 683.34136.

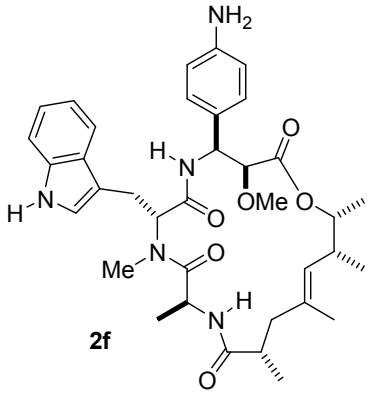


Chondramide 2d (F). To a stirred solution of compound **22d** (30 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) was added TFA (40 µL, 0.54 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo. For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in DMF (36 mL) and *i*Pr_2NEt (24 µL, 0.144 mmol), HOBt (17 mg, 0.126 mmol) and TBTU (29 mg, 0.126 mmol) were added. The solution was stirred at room temperature for 20 h and then diluted with water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (20 mL), water (20 mL), saturated $NaHCO_3$ solution (20 mL), water (2 × 20 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/acetone, 2:1) of the residue to give depsipeptide **2d** (9.00 mg, 31% over three steps) as a colorless foam. R_f (petroleum ether/acetone, 2:1) 0.16; $[\alpha]^{20}_D$ = +13.3 (*c* 0.67, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.87 (d, *J* = 6.1 Hz, 3H, 7-CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 0.92 (d, *J* = 6.6 Hz, 3H, 6-CH_3), 1.09 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 1.70 (s, 3H, 4-CH_3), 2.05 (dd, *J* = 13.0, 3.2 Hz, 1H, CH_2), 2.16–2.27 (m, 1H, CH_2), 2.46–2.58 (m, 1H, 6-H), 2.63–2.73 (m, 1H, 2-H), 3.07 (d, *J* = 8.3 Hz, 2H, Trp CH_2), 3.10 (s, 3H, NCH_3), 3.12 (s, 3H, OCH_3), 3.82 (d, *J* = 10.1 Hz, 1H, C*H*OCH_3), 4.48–4.55 (m, 1H, 7-H), 4.78–4.84 (m, 2H, Ala CH, 5-H), 5.05 (d, *J* = 10.1 Hz, 1H, β-Tyr CH), 5.52 (dd, *J* = 8.1, 8.0 Hz, 1H, Trp CH), 6.79 (s, 1H, Trp H_{ar}), 6.88–6.94 (m, 2H, β-Tyr H_{ar}), 6.95–7.00 (m, 1H, Trp H_{ar}), 7.03–7.09 (m, 3H, β-Tyr H_{ar}, Trp H_{ar}), 7.25 (d, *J* = 8.1 Hz, 1H, Trp H_{ar}), 7.58 (d, *J* = 7.8 Hz, 1H, Trp H_{ar}); ^{13}C NMR (100 MHz, CD_3OD): δ = 16.0 (4-CH_3), 18.0 (6-CH_3), 18.5 (Ala CH_3), 19.0 (7-CH_3, 2-CH_3), 26.7 (Trp CH_2), 30.9 (NCH_3), 38.7 (C-6), 40.2 (C-2), 45.9 (Ala CH), 46.2 (CH_2), 55.5 (β-Tyr CH), 57.0 (Trp CH), 58.2 (OCH_3), 79.4 (C-7), 83.1 (*C*HOCH_3), 109.9 (Trp C_{ar}), 112.2 (Trp C_{ar}), 115.4 (d, *J* = 21.2 Hz, β-Tyr C_{ar}), 119.4 (Trp C_{ar}), 119.6 (Trp C_{ar}), 122.3 (Trp C_{ar}), 124.5 (Trp C_{ar}), 128.5 (Trp C_{ar}), 129.0 (C-5), 130.2 (d, *J* = 8.1 Hz, β-Tyr C_{ar}), 134.7 (C-4), 136.4 (d, *J* = 2.9 Hz, β-Tyr C_{ar}), 137.9 (Trp C_{ar}), 171.2 (CO), 173.3 (CO), 174.8 (CO), 176.9 (CO); HRMS (ESI): *m/z*: calcd for $C_{36}H_{45}FN_4O_6$ $[M+Na]^+$: 671.32153; found: 671.32177.



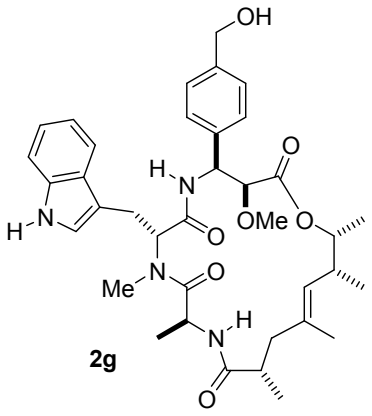
2e

Chondramide 2e (NO_2). To a stirred solution of compound **22e** (62.7 mg, 0.0738 mmol) in CH_2Cl_2 (2.2 mL) was added TFA (0.22 mL, 0.34 g, 2.98 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo (TLC control: CH_2Cl_2/MeOH/NH_3, 10:1:0.1). For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in DMF (30 mL) and *i*Pr_2NEt (64 µL, 47.7 mg, 0.369 mmol, 5 equiv), HOBt (19.9 mg, 0.147 mmol, 2 equiv) and TBTU (47.4 mg, 0.147 mmol, 2 equiv) were added. The solution was stirred at room temperature for 20 h and then diluted with water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (20 mL), water (20 mL), saturated $NaHCO_3$ solution (20 mL), water (2 × 20 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 1:3 to 0:1) to give depsipeptide **2e** (27.3 mg, 48%) as a colorless foam. R_f (EtOAc) 0.41; $[\alpha]^{20}_D$ = +18.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3H, CH_3), 0.85 (d, *J* = 6.1 Hz, 3H, CH_3), 1.07 (d, *J* = 6.8 Hz, 3H, CH_3), 1.17 (d, *J* = 6.8 Hz, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.88 (d, *J* = 13.1 Hz, 1H, CH_2), 2.36–2.51 (m, 3H, 2 CH, CH_2), 2.95 (s, 3H, NCH_3), 3.17 (dd, *J* = 15.2, 8.6 Hz, 1H, CH_2), 3.22 (s, 3H, OCH_3), 3.31 (dd, *J* = 15.2, 7.8 Hz, 1H, CH_2), 3.75 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 4.77–4.83 (m, 2H, Ala CH, CO_2CH), 4.90 (d, *J* = 9.1 Hz, 1H, =CH), 5.30 (t, *J* = 8.3 Hz, 1H, β-Tyr CH), 5.60 (t, *J* = 8.1 Hz, 1H, Trp CH), 6.50 (d, *J* = 7.3 Hz, 1H, Ala NH), 6.82 (s, 1H, Trp H_{Ar}), 7.06 (d, *J* = 8.8 Hz, 1H, β-Tyr NH), 7.10 (ddd, *J* = 8.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.17 (ddd, *J* = 8.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.24 (d, *J* = 8.6 Hz, 2H, Ar), 7.32 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.59 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 8.06 (d, *J* = 8.6 Hz, 2H, Ar), 8.11 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 16.6, 17.3, 18.6, 20.0, 23.6 (CH_2), 30.2 (NCH_3), 37.0, 40.2, 44.1 (CH_2), 45.2 (Ala CH), 54.4 (β-Tyr CH), 56.0 (Trp CH), 58.2 (OCH_3), 76.8 (CO_2*C*H), 81.9 (*C*HOCH_3), 110.2 (quat. Trp), 111.2, 118.5, 119.6, 122.2, 122.3, 123.4, 127.1 (quat. Trp), 127.8 (=CH), 127.9, 134.3 (=C<), 136.1 (quat. Trp), 144.5, 147.3, 169.77, 169.82, 174.1, 174.5; HMRS (ESI): *m/z*: calcd for $C_{36}H_{45}N_5O_8$ [*M*+Na]$^+$: 698.31603; found: 698.31672.



2f

Chondramide 2f (NH_2). *By catalytic hydrogenation*: A solution of chondramide **2e** (6.1 mg, 9.03 μmol) in methanol (0.5 mL) was hydrogenated overnight in a round bottom flask connected to a hydrogen filled balloon, using 10% Pd on carbon (TLC control: CH_2Cl_2/MeOH, 10:1). Upon complete conversion, the solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/MeOH, 30:1 to 20:1) to afford chondramide **2f** (2.7 mg, 47%) as white foam. A mixed fraction, containing **2f** and another unknown compound as major components was also isolated. Complete conversion was observed, but the reaction was not very clean, likely because of formation of RNO and/or RNHOH, as suggested by LC/MS examination of the mixed fraction. No evidence for competitive hydrogenation of the double bond was found.
By reduction with sodium dithionite: Alternatively, reduction of chondramide **2e** (5.8 mg, 8.58 μmol) was carried out in solution in THF (0.5 mL), H_2O (0.5 mL) in the presence of $Na_2S_2O_4$ (20 mg, 0.115 mmol) overnight at room temperature. Conversion was high but not complete. The reaction mixture was diluted with saturated NaCl solution and EtOAc with addition of some saturated $NaHCO_3$ solution. The water phase was extracted once more with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and evaporated. The desired NH_2-chondramide **2f** (2 mg, 36%) was isolated successfully by flash chromatography (CH_2Cl_2/MeOH 30:1 to 20:1) as a white foam. R_f (CH_2Cl_2/MeOH 20:1) 0.26. $[\alpha]^{20}_D$ = +24.9 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.3 Hz, 3H, CH_3), 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 1.03 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.15 (d, *J* = 7.1 Hz, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.80 (d, *J* = 13.9 Hz, 1H, CH_2), 2.33–2.40 (m, 2H, 2 CH), 2.53 (d, *J* = 10.4, 13.6 Hz, 1H, CH_2), 2.94 (s, 3H, NCH_3), 3.14 (dd, *J* = 15.5, 9.2 Hz, 1H, CH_2), 3.23 (s, 3H, OCH_3), 3.27 (dd, *J* = 15.5, 6.8 Hz, 1H, CH_2), 3.68 (bs, 2H, NH_2), 3.75 (d, *J* = 7.3 Hz, 1H, C*H*OCH_3), 4.77–4.84 (m, 2H, Ala CH, 7-H), 4.90 (d, *J* = 8.8 Hz, 1H, =CH), 5.25 (dd, *J* = 7.3, 9.1 Hz, 1H, β-Tyr CH), 5.60 (dd, *J* = 7.1, 9.1 Hz, 1H, Trp CH), 6.58 (d, *J* = 7.3 Hz, 1H, Ala NH), 6.58 (d, *J* = 8.3 Hz, 2H, Ar), 6.81 (d, *J* = 2.2 Hz, 1H, Trp H_{Ar}), 6.92–6.96 (m, 3H, β-Tyr NH, Ar), 7.11 (ddd, *J* = 8.1, 7.8, 1.0 Hz, 1H, Trp H_{Ar}), 7.17 (ddd, *J* = 8.1, 7.8, 1.0 Hz, 1H, Trp H_{Ar}), 7.30 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 7.90 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 7.87 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 16.6, 17.6, 18.6, 20.5, 23.3 (CH_2), 30.1 (NCH_3), 37.1, 40.3, 43.8 (CH_2), 45.3 (Ala CH), 53.9 (β-Tyr CH), 55.7 (Trp CH), 58.0 (OCH_3), 77.2 (CO_2*C*H), 82.6 (*C*HOCH_3), 110.7 (quat. Trp), 111.0, 115.0 (2C, Ar), 118.6, 119.4, 122.05, 122.11, 127.2 (quat. Trp), 127.7 (quat. Ar), 127.9 (2C, Ar), 128.4 (=CH), 134.1 (=C<), 136.1 (quat. Trp), 145.9, 169.6, 170.6, 174.0, 174.5; HMRS (ESI): *m/z*: calcd for $C_{36}H_{47}N_5O_6$ $[M+Na]^+$: 668.34186; found: 668.34224.



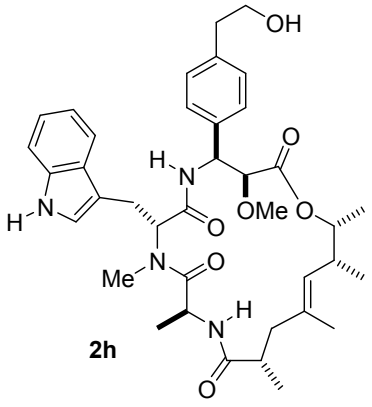
2g

Chondramide 2g (CH_2OH). To a stirred solution of compound **22g** (64.7 mg, which corresponds to ~58.9 mg of pure peptide, 0.0621 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.2 mL, 0.307 g, 2.69 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo (TLC control: CH_2Cl_2/MeOH/NH_3, 10:1:0.1). For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated

in vacuo each time. NMR examination indicated complete deprotection and installation of $CH_2OC(O)CF_3$ in place of CH_2OTBS (δ = 5.25, s, 2H, $ArCH_2OC(O)CF_3$). The crude product was dissolved in DMF (25 mL, that corresponds to 0.0025M concentration of the starting amino acid) and iPr$_2$NEt (54 μL, 40 mg, 0.310 mmol, 5 equiv), HOBt (16.7 mg, 0.124 mmol, 2 equiv) and TBTU (39.9 mg, 0.124 mmol, 2 equiv) were added. The solution was stirred at room temperature for 20 h and then diluted with water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (20 mL), water (20 mL), diluted K_2CO_3 solution (20 mL, at this point trifluoroacetic ester moiety is hydrolyzed), water (2 × 20 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to give depsipeptide **2g** (8.1 mg, 20%) as a colorless foam.

Note. $ArCH_2OTFA$ is hydrolyzed in a few minutes in weakly alkaline media during washings (as was the case in synthesis of **2h**). But in this case the less polar product (on TLC), which was initially assumed to be $ArCH_2OTFA$ ester, in fact was stable to hydrolysis and was eventually proved to be the $ArCH_2OBt$ ether!). Obviously, the benzylic trifluoroacetate has led to extensive formation of the nucleophilic substitution product due to enhanced susceptibility to nucleophilic attack.

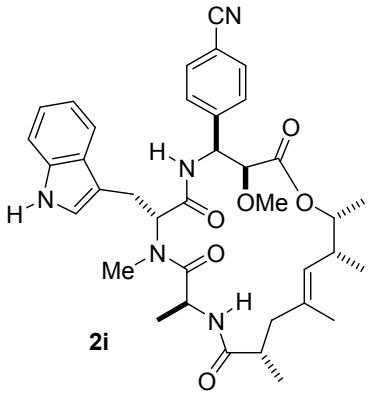
2g: R_f (CH_2Cl_2/MeOH 20:1) 0.14; $[\alpha]^{20}_D$ = +23.4 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.3 Hz, 3H, CH_3), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.08 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.16 (d, *J* = 6.6 Hz, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.87 (d, *J* = 13.1 Hz, 1H, CH_2), 2.27 (bs, 1H, OH), 2.35–2.42 (m, 2H, 2 CH), 2.48 (dd, *J* = 13.1, 11.1 Hz, 1H, CH_2), 2.98 (s, 3H, NCH_3), 3.00 (dd, *J* = 15.2, 7.8 Hz, 1H, CH_2), 3.21 (s, 3H, OCH_3), 3.27 (dd, *J* = 15.2, 8.1 Hz, 1H, CH_2), 3.78 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 4.68 (s, 2H, $ArCH_2$), 4.72–4.78 (m, 1H, 7-H), 4.79–4.86 (m, 1H, Ala CH), 4.89 (d, *J* = 9.1 Hz, 1H, =CH), 5.26 (dd, *J* = 8.1, 8.8 Hz, 1H, β-Tyr CH), 5.49 (dd, *J* = 7.8, 8.1 Hz, 1H, Trp CH), 6.54 (d, *J* = 7.8 Hz, 1H, Ala NH), 6.56 (d, *J* = 2.3 Hz, 1H, Trp H_{Ar}), 6.82 (d, *J* = 9.4 Hz, 1H, β-Tyr NH), 7.07–7.11 (m, 3H, Trp H_{Ar}, Ar), 7.16 (ddd, *J* = 8.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.24 (d, *J* = 8.1 Hz, 2H, Ar), 7.29 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.58 (d, *J* = 7.8 Hz, 1H, Trp H_{Ar}), 8.13 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 16.4, 17.7, 18.8, 20.0, 23.9 (CH_2), 30.2 (NCH_3), 37.2, 40.2, 44.2 (CH_2), 45.2 (Ala CH), 54.5 (β-Tyr CH), 55.9 (Trp CH), 58.1 (OCH_3), 65.1 (CH_2O), 76.5 (CO_2*C*H), 82.1 (*C*HOCH_3), 109.8 (quat. Trp), 111.2, 118.4, 119.3, 121.9, 122.5, 127.0 (quat. Trp), 127.2 (2C, Ar), 127.5 (2C, Ar), 128.2 (=CH), 133.1 (=C<), 136.1, 137.8, 140.0, 169.4, 170.5, 173.9, 174.4; HMRS (ESI): *m/z*: calcd for $C_{37}H_{48}N_4O_7$ $[M+Na]^+$: 683.34152; found: 683.34136.



2h

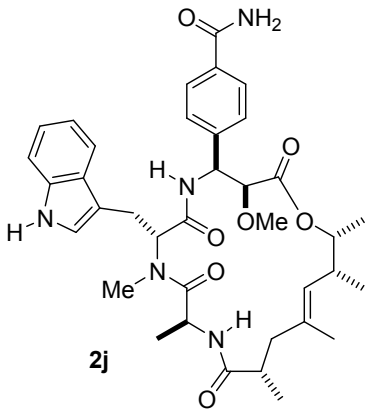
Chondramide 2h (CH_2CH_2OH). To a stirred solution of depsipeptide **22h** (18.2 mg, 0.0189 mmol) in CH_2Cl_2 (0.6 mL) was added TFA (0.06 mL, 0.092 g, 0.808 mmol) at 0 °C. The reaction

mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo (TLC control: CH_2Cl_2/MeOH/NH_3, 10:1:0.1). For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo. NMR examination indicated complete deprotection and installation of $CH_2CH_2OC(O)CF_3$ in place of CH_2CH_2OTBS. The crude product was dissolved in DMF (7.50 mL, that corresponds to 0.0025M concentration of the starting amino acid) and *i*Pr_2NEt (16 µL, 11.8 mg, 0.092 mmol, 5 equiv), HOBt (5.1 mg, 0.038 mmol, 2 equiv) and TBTU (12.1 mg, 0.038 mmol, 2 equiv) were added. The solution was stirred at room temperature for 20 h and then diluted with water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (10 mL), water (10 mL), diluted K_2CO_3 solution (10 mL, at this point complete hydrolysis of trifluoroacetic ester moiety should be secured), water (2 × 10 mL) and saturated NaCl solution (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. In case of incomplete hydrolysis, the residue was dissolved in MeOH, catalytic amount of K_2CO_3 was added and the silution stirred for 5 minutes until disappearance of the trifluoroacetate residue (R_f (EtOAc) 0.4, ^{1}H NMR ($CDCl_3$): δ = 4.50 (t, C*H*$_2$OC(O)CF_3)). But normally, the trifluoroacetate is hydrolized within a few minutes in weakly alkaline media during washings, which was also observed by TLC. The crude product was purified by flash chromatography (EtOAc) to give depsipeptide **2h** (7.7 mg, 60%) as a colorless foam. R_f (CH_2Cl_2/MeOH 20:1) 0.14; R_f (EtOAc) 0.3; $[\alpha]^{20}_D$ = +6.3 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.3 Hz, 3H, CH_3), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.14 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.16 (d, *J* = 6.6 Hz, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.81 (bt, *J* = 4.3 Hz, 1H, OH), 1.91 (d, *J* = 11.4 Hz, 1H, CH_2), 2.35–2.47 (m, 3H, 2 CH, CH_2), 2.87 (t, *J* = 6.1 Hz, 2H, ArCH_2), 2.92 (dd, *J* = 14.5, 6.6 Hz, 1H, CH_2), 3.02 (s, 3H, NCH_3), 3.18 (s, 3H, OCH_3), 3.28 (dd, *J* = 14.5, 8.9 Hz, 1H, CH_2), 3.75 (d, *J* = 8.7 Hz, 1H, C*H*OCH_3), 3.94–4.02 (m, 2H, C*H*$_2$OH), 4.68–4.74 (m, 1H, 7-H), 4.80–4.86 (m, 1H, Ala CH), 4.88 (d, *J* = 9.4 Hz, 1H, =CH), 5.22 (dd, *J* = 8.9, 8.9 Hz, 1H, β-Tyr CH), 5.41 (dd, *J* = 6.9, 9.2 Hz, 1H, Trp CH), 6.46–6.49 (m, 2H, Ala NH, Trp H_{Ar}), 6.52 (d, *J* = 7.9 Hz, 1H, β-Tyr NH), 7.02 (d, *J* = 7.9 Hz, 2H, Ar), 7.08–7.17 (m, 4H, Trp H_{Ar}, Ar), 7.27 (d, 1H, Trp H_{Ar}), 7.59 (d, *J* = 7.6 Hz, 1H, Trp H_{Ar}), 8.43 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.27, 16.30, 17.8, 18.9, 19.7, 24.4 (CH_2), 30.3 (NCH_3), 37.4, 38.6 (ArCH_2), 40.1, 44.4 (CH_2), 45.1 (Ala CH), 54.5 (β-Tyr CH), 56.1 (Trp CH), 58.0 (OCH_3), 63.5 (CH_2OH), 76.7 (CO_2*C*H), 82.1 (*C*HOCH_3), 109.3 (quat. Trp), 111.2, 118.3, 119.1, 121.7, 122.8, 126.9 (quat. Trp), 127.2 (2C, Ar), 128.2 (=CH), 129.1 (2C, Ar), 133.7 (=C<), 136.1 (quat. Trp), 136.6, 138.2, 169.2, 170.6, 173.7, 174.2; HMRS (ESI): *m/z*: calcd for $C_{38}H_{50}N_4O_7$ [*M*+Na]$^+$: 697.35717; found: 697.35723.



Chondramide 2i (CN). To a stirred solution of depsipeptide **22i** (24.5 mg, 0.0295 mmol) in CH_2Cl_2 (0.9 mL) was added TFA (0.09 mL, 0.138 g, 1.21 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, the solvent was removed in vacuo (TLC control: CH_2Cl_2/MeOH/NH_3, 10:1:0.1). For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in

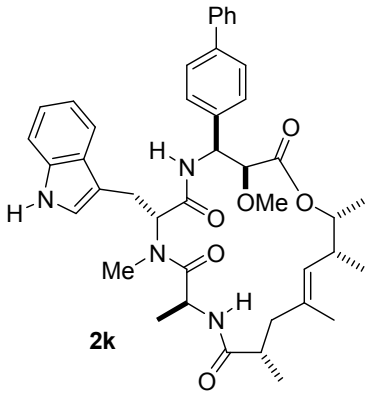
DMF (11.8 mL, that corresponds to 0.0025M concentration of the starting amino acid) and *i*Pr_2NEt (26 µL, 19.3 mg, 0.149 mmol, 5 equiv), HOBt (8.0 mg, 0.059 mmol, 2 equiv) and TBTU (18.9 mg, 0.059 mmol, 2 equiv) were added. The solution was stirred at room temperature for 20 h and then diluted with water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (20 mL), water (20 mL), saturated $NaHCO_3$ solution (20 mL), water (2 × 20 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 1:3 to 0:1 or petroleum ether/acetone, 3:2) to give depsipeptide **2i** (8.7 mg, 45%) as a colorless foam. In order to obtain pure **2i**, the chromatography was done twice. R_f (EtOAc) 0.4; $[\alpha]^{20}_D$ = +20.1 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.4 Hz, 3H, CH_3), 0.85 (d, *J* = 6.9 Hz, 3H, CH_3), 1.05 (d, *J* = 6.9 Hz, 3H, CH_3), 1.17 (d, *J* = 6.6 Hz, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.85 (d, *J* = 13.5 Hz, 1H, CH_2), 2.35–2.44 (m, 2H, 2 CH), 2.50 (dd, *J* = 10.5, 13.5 Hz, 1H, CH_2), 2.94 (s, 3H, NCH_3), 3.10 (dd, *J* = 15.2, 8.6 Hz, 1H, CH_2), 3.23 (s, 3H, OCH_3), 3.30 (dd, *J* = 15.2, 7.4 Hz, 1H, CH_2), 3.75 (d, *J* = 7.6 Hz, 1H, C*H*OCH_3), 4.76–4.83 (m, 2H, Ala CH, 7-H), 4.89 (d, *J* = 8.9 Hz, 1H, =CH), 5.30 (dd, *J* = 8.1, 8.3 Hz, 1H, β-Tyr CH), 5.62 (t, *J* = 7.4, 8.6 Hz, 1H, Trp CH), 6.49 (d, *J* = 7.1 Hz, 1H, Ala NH), 6.85 (d, *J* = 2.3 Hz, 1H, Trp H_{Ar}), 7.08–7.13 (m, 2H, β-Tyr NH, Trp H_{Ar}), 7.19 (ddd, *J* = 8.1, 7.1, 0.8 Hz, 1H, Trp H_{Ar}), 7.24 (d, *J* = 8.6 Hz, 2H, Ar), 7.33 (d, *J* = 8.1 Hz, 1H, Trp H_{Ar}), 7.53 (d, *J* = 8.4 Hz, 2H, Ar), 7.60 (d, *J* = 7.9 Hz, 1H, Trp H_{Ar}), 7.98 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 16.7, 17.3, 18.6, 20.2, 23.4 (CH_2), 30.2 (NCH_3), 37.0, 40.2, 44.0 (CH_2), 45.2 (Ala CH), 54.4 (β-Tyr CH), 55.9 (Trp CH), 58.2 (OCH_3), 76.5 (CO_2*C*H), 81.9 (*C*HOCH_3), 110.4 (quat. Trp), 111.2, 111.5, 118.55, 118.60, 119.6, 122.16, 122.20, 127.1 (quat. Trp), 127.8 (=CH), 127.8, 132.1, 134.4 (=C<), 136.1 (quat. Trp), 143.4, 169.82, 169.92, 174.2, 174.5; HMRS (ESI): *m/z*: calcd for $C_{37}H_{45}N_5O_6$ [*M*+Na]$^+$: 678.32621; found: 678.32685.



2j

Chondramide 2j ($CONH_2$). To a solution of chondramide **2i** (4.5 mg, 6.87 µmol) in DMSO (0.1 mL) were added at 10 °C K_2CO_3 (10 mg, 0.072 mmol) and 30% aqueous H_2O_2 (0.01 mL). The reaction mixture was stirred for 5–10 min when TLC (EtOAc) showed complete conversion. The reaction mixture was diluted with water (0.5 mL) and extracted twice with EtOAc. The combined organic extracts were washed with water, saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue purified by flash chromatography (CH_2Cl_2/MeOH, 15:1 to 10:1) to afford chondramide **2j** (3 mg, 67%) as white foam (contaminated with 1.9 % w/w DMSO). $[\alpha]^{20}_D$ = +26.7 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.3 Hz, 3H, CH_3), 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 1.09 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 1.17 (d, *J* = 6.8 Hz, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.87 (d, *J* = 13.4 Hz, 1H, CH_2), 2.35–2.42 (m, 2H, 2 CH), 2.48 (dd, *J* = 10.9, 13.4 Hz, 1H, CH_2), 2.98 (s, 3H, NCH_3), 3.03 (dd, *J* = 14.9, 8.1 Hz, 1H, CH_2), 3.21 (s, 3H, OCH_3), 3.30 (dd, *J* = 14.9, 8.1 Hz, 1H, CH_2), 3.77 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 4.74–4.86 (m, 2H, Ala CH, 7-H), 4.89 (d, *J* = 9.1 Hz, 1H, =CH), 5.26 (dd, *J* = 8.3, 8.6 Hz, 1H, β-Tyr CH), 5.57 (t, *J* = 8.1, 8.1 Hz, 1H, Trp CH), 5.68 (bs, 1H, $CONH_2$), 6.14 (bs, 1H, $CONH_2$), 6.54 (d, *J* = 7.6 Hz, 1H, Ala NH), 6.70 (d, *J* =

2.3 Hz, 1H, Trp H_{Ar}), 6.98 (d, J = 8.8 Hz, 1H, β-Tyr NH), 7.09–7.19 (m, 4H, Trp H_{Ar}, Ar), 7.33 (d, J = 7.8 Hz, 1H, Trp H_{Ar}), 7.60–7.64 (d+d, 3H, Trp H_{Ar}, Ar), 8.14 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 16.6, 17.6, 18.8, 20.1, 23.8 (CH_2), 30.2 (NCH_3), 37.1, 40.2, 44.1 (CH_2), 45.2 (Ala CH), 54.5 (β-Tyr CH), 56.0 (Trp CH), 58.2 (OCH_3), 77.2 (CO_2CH), 82.0 ($CHOCH_3$), 110.2, 111.3, 118.5, 119.4, 122.1, 122.3, 127.1, 127.2, 127.4, 128.1, 132.6, 134.1 (=C<), 136.1, 142.3, 169.1, 169.6, 170.2, 174.0, 174.4; HMRS (ESI): *m/z*: calcd for $C_{37}H_{47}N_5O_7$ $[M+Na]^+$: 696.33677; found: 696.337415.

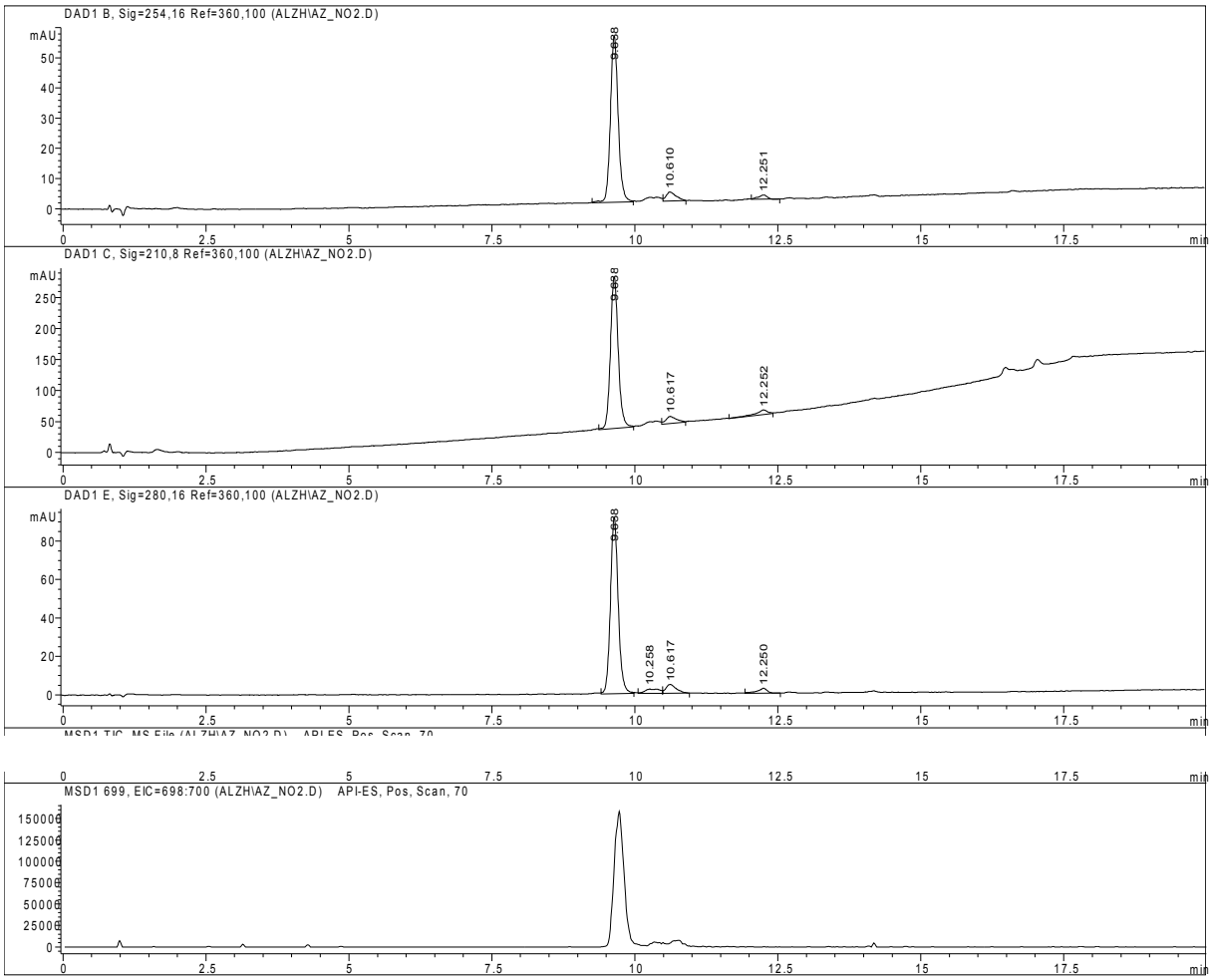


2k

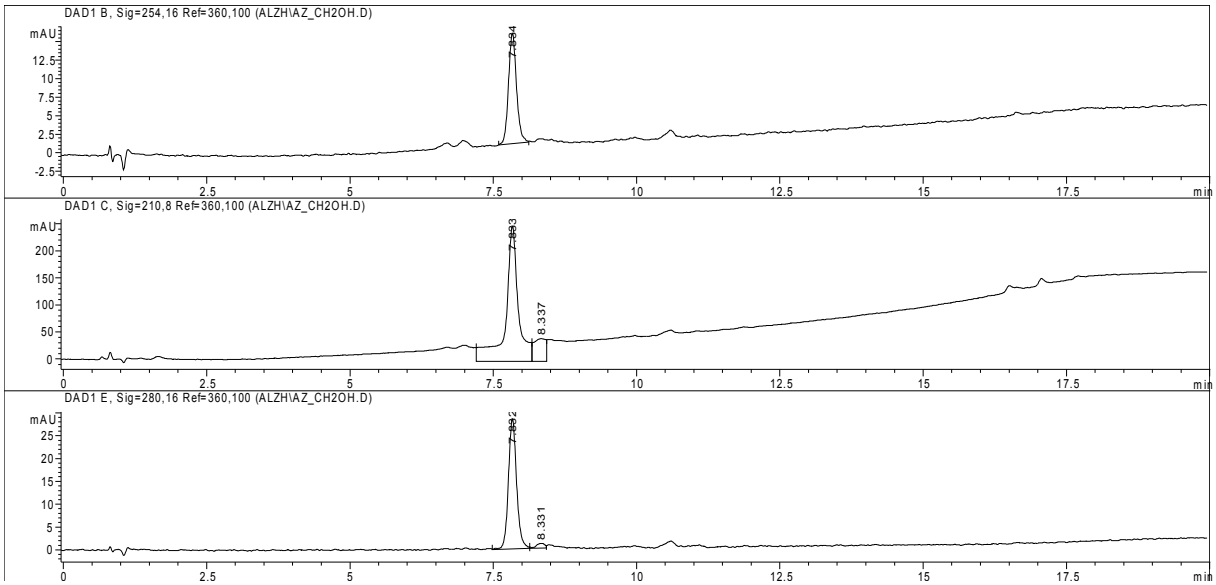
Chondramide 2k (Ph). To a stirred solution of compound **22k** (62.4 mg, 0.0708 mmol) in CH_2Cl_2 (2.1 mL) was added TFA (0.21 mL, 0.322 g, 2.82 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 21 h, the solvent was removed in vacuo [TLC control: CH_2Cl_2/MeOH/NH_3, 10:1:0.1, R_f (amino ester intermediate) 0.47, (amino acid) 0.2]. For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in DMF (35 mL, that corresponds to 0.002M concentration of the starting amino acid) and iPr$_2$NEt (62 µL, 46.0 mg, 0.356 mmol, 5 equiv), HOBt (14.3 mg, 0.106 mmol, 2 equiv) and TBTU (34.1 mg, 0.106 mmol, 2 equiv) were added. The solution was stirred at room temperature for 20 h and then diluted with water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (20 mL), water (20 mL), saturated $NaHCO_3$ solution (20 mL), water (2 × 20 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc) to give depsipeptide **2k** (27.3 mg, 54%) as a colorless foam. R_f (EtOAc) 0.4; $[\alpha]^{20}_D$ = +20.3 (*c* 2.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, J = 6.6 Hz, 3H, CH_3), 0.84 (d, J = 6.1 Hz, 3H, CH_3), 1.03 (d, J = 6.8 Hz, 3H, CH_3), 1.16 (d, J = 6.8 Hz, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.81 (d, J = 13.9 Hz, 1H, CH_2), 2.33–2.40 (m, 3H, 2 CH), 2.55 (dd, J = 13.9, 10.1 Hz, 1H, CH_2), 2.95 (s, 3H, NCH_3), 3.16 (dd, J = 15.7, 9.2 Hz, 1H, CH_2), 3.27 (s, 3H, OCH_3), 3.30 (dd, J = 15.2, 7.0 Hz, 1H, CH_2), 3.86 (d, J = 7.1 Hz, 1H, C*H*OMe), 4.78–4.86 (m, 2H, Ala CH, 7-H), 4.91 (d, J = 8.8 Hz, 1H, =CH), 5.41 (dd, J = 9.1, 7.1, Hz, 1H, β-Tyr CH), 5.68 (dd, J = 9.2, 7.0 Hz, 1H, Trp CH), 6.60 (d, J = 7.3 Hz, 1H, Ala NH), 6.84 (d, J = 2.0 Hz, 1H, Trp H_{Ar}), 7.09–7.18 (m, 3H, β-Tyr NH, Trp H_{Ar}), 7.23–7.36 (m (d+d+t), 4H, Ar, Trp H_{Ar}), 7.43 (dd, J = 7.1, 7.8 Hz, 2H, Ar), 7.50 (d, J = 8.3 Hz, 2H, Ar), 7.55 (d, J = 7.1 Hz, 2H, Ar), 7.62 (d, 1H, J = 7.6 Hz, Trp H_{Ar}), 8.05 (s, 1H, Trp NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 16.6, 17.5, 18.6, 20.5, 23.2 (CH_2), 30.1 (NCH_3), 37.0, 40.3, 43.8 (CH_2), 45.3 (Ala CH), 54.2 (β-Tyr CH), 55.7 (Trp CH), 58.0 (OCH_3), 75.9 (CO_2CH), 82.4 ($CHOCH_3$), 110.5 (quat. Trp), 111.1, 118.6, 119.4, 122.0, 122.1, 127.0, 127.1 (quat. Trp), 127.2, 127.3, 127.4 (=CH), 128.4, 128.8, 134.2 (=C<), 136.1 (quat. Trp), 136.6, 140.55, 140.58, 169.9, 170.3, 174.1, 174.6; HMRS (ESI): *m/z*: calcd for $C_{42}H_{50}N_4O_6$ $[M+Na]^+$: 729.36226; found: 729.36180.

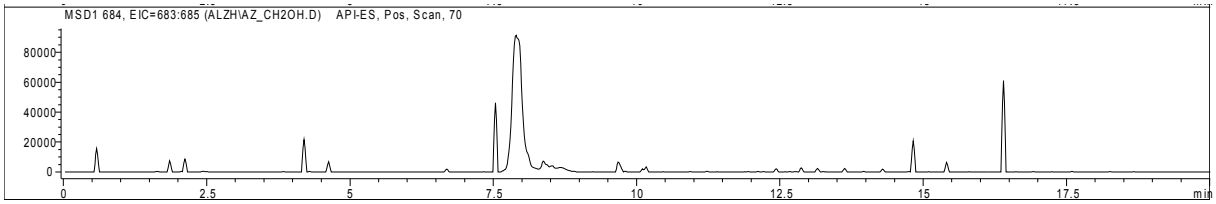
LC-MS-traces of some of the chondramide A analogues

Chon NO_2 **2e**

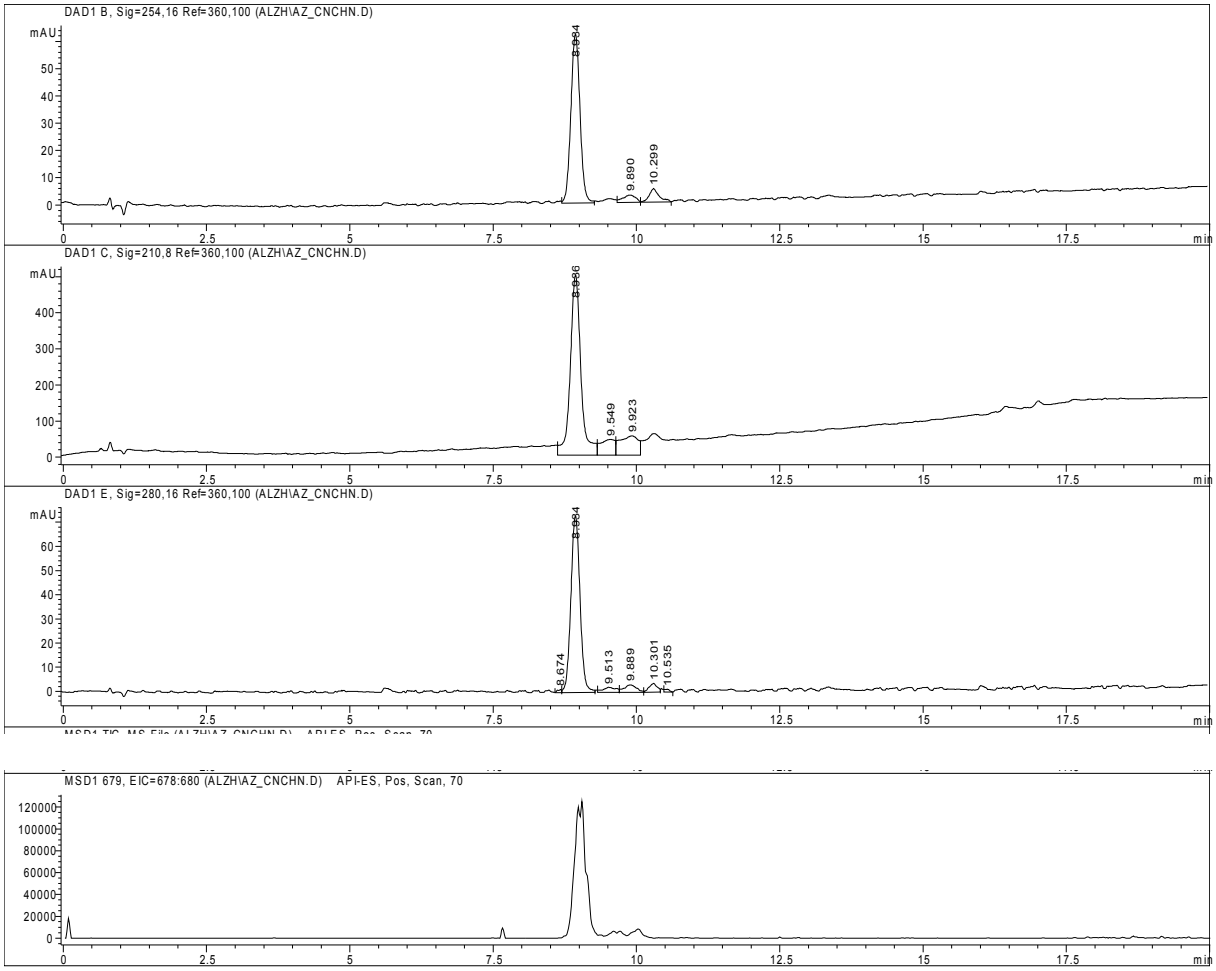


Chon CH_2OH **2g**

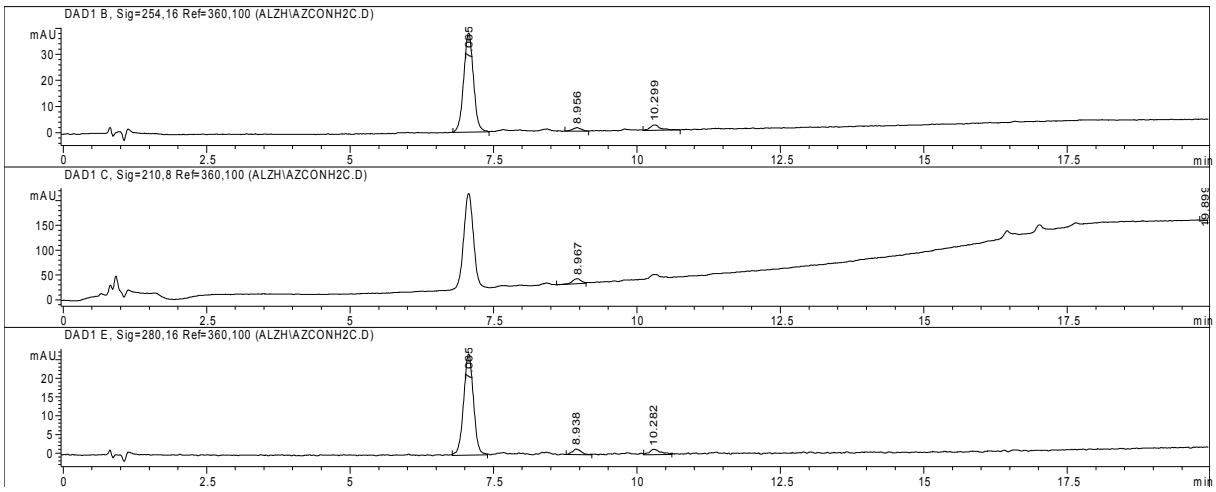


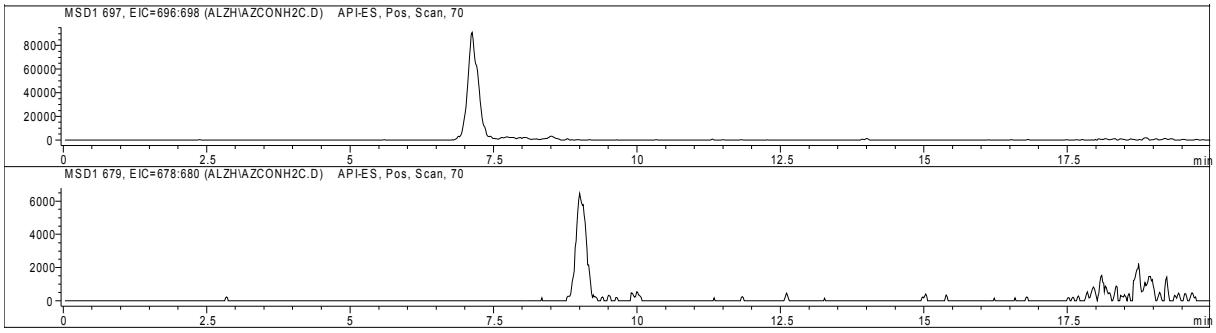


Chon CN **2i**

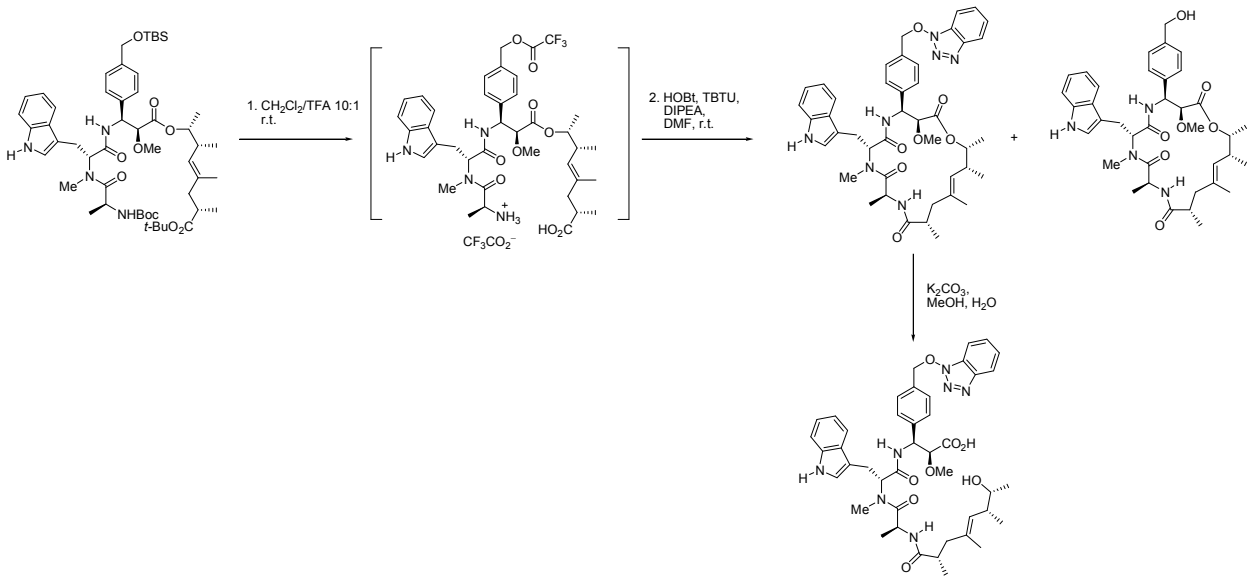


Chon $CONH_2$ **2j** (mixture of the hydrolysis reaction, the Chon CN peak is at ~8.94 min)





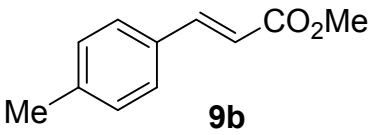
Proof of structure of benzotriazolyl ether



Alkaline hydrolysis (K_2CO_3, MeOH, H_2O, rt, overnight) of the less polar product, which was initially assumed to be the CH_2OTFA ester (because of the high shift benzylic methylene proton, δ = 5.49, s, overlapped, 2H, ArCH_2OBt), did not lead to the desired chondramide, and the polar compound, that obviously must be some open-chained chondramide derivative (acid), was isolated by column chromatography (CH_2Cl_2/MeOH/AcOH 10:1:0.05; R_f in 10:1:0.1 is 0.38). NMR examination revealed that the high shift benzylic methylene proton (δ = 5.48, s, 2H, ArCH_2OBt) is still present. It became clear that during macrolactamization, the trifluororacetate changed to a functionality stable to hydrolysis. This could be only benzotriazolyl ether, resulting from nucleophilic attack of HOBt present in excess in the reaction mixture. Unambigouosly, this was proved by HRMS analysis of the acid. HMRS (ESI): *m/z*: calcd for $C_{43}H_{53}N_7O_8$ $[M+Na]^+$: 818.38479; found: 818.38525.

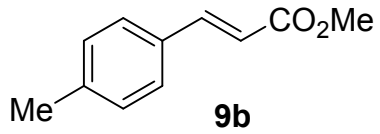
^{1}H and ^{13}C NMR spectra of the products

^{1}H NMR (400 MHz) spectrum of enoate **9b** in $CDCl_3$



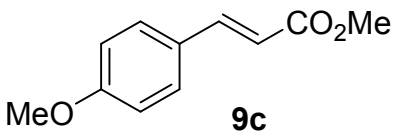
9b

^{13}C NMR (100 MHz) spectrum of enoate **9b** in $CDCl_3$



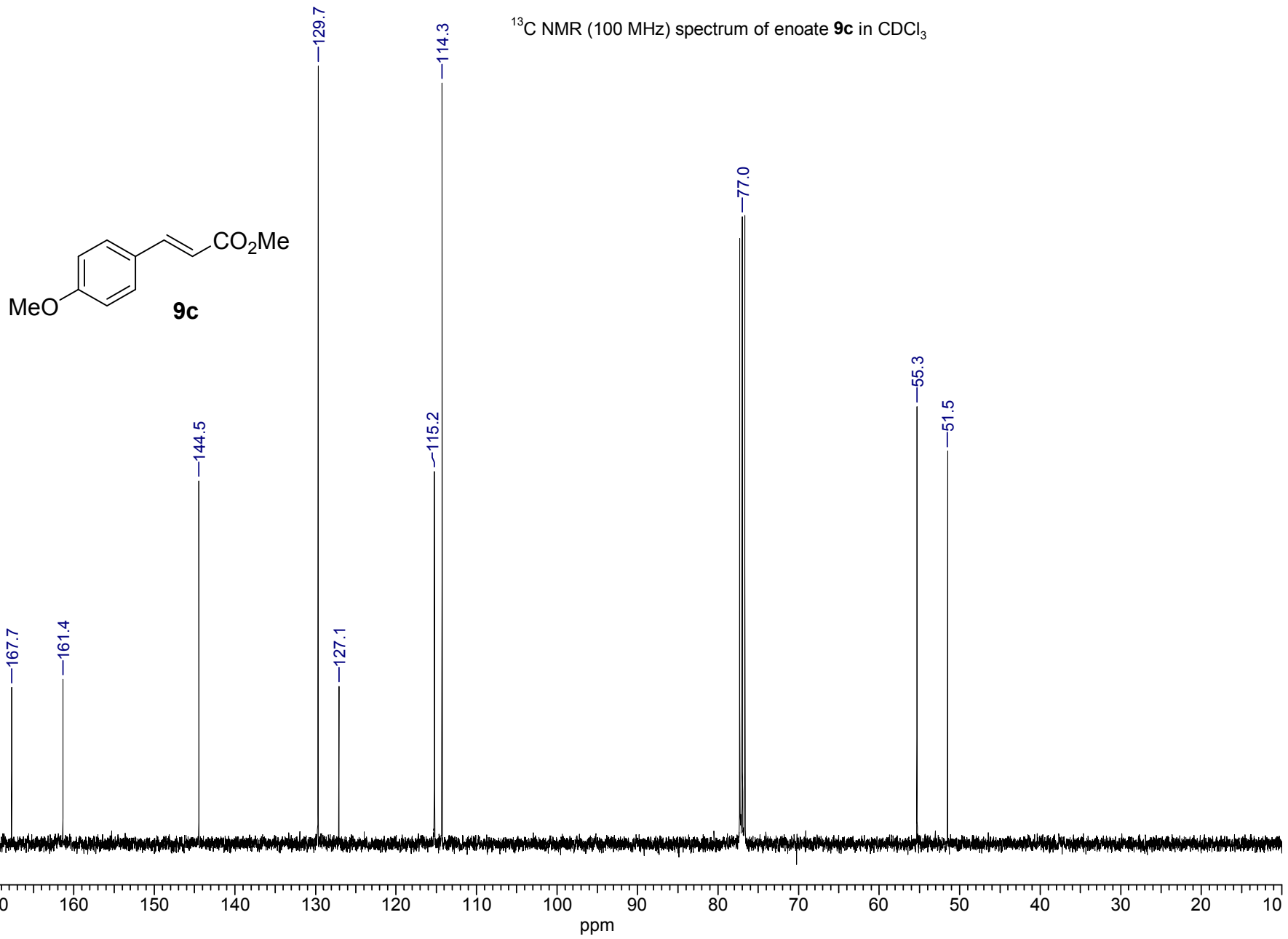
9b

^{1}H NMR (400 MHz) spectrum of enoate **9c** in $CDCl_3$

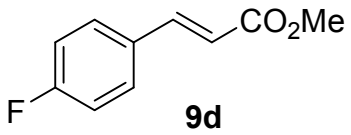


9c

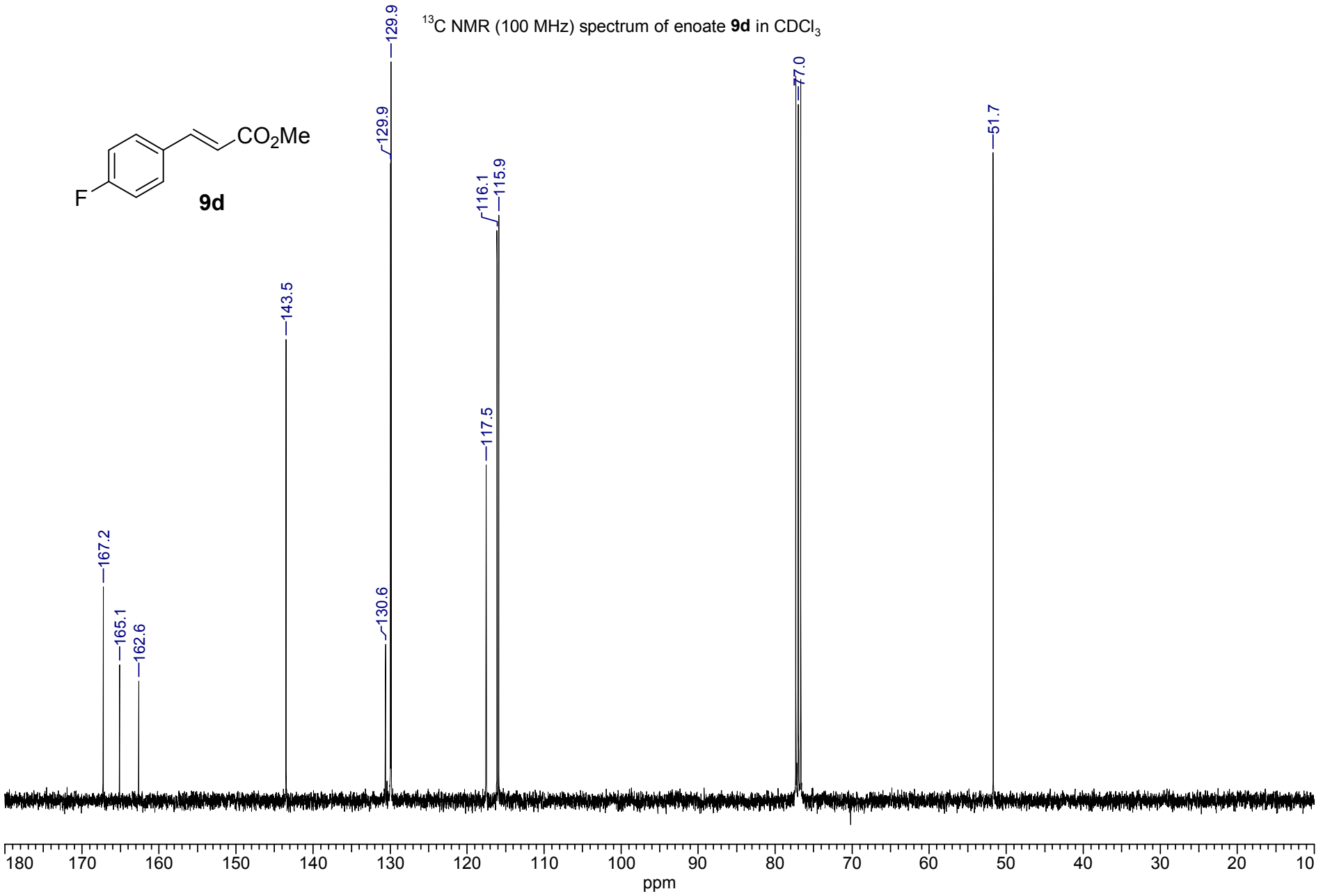
^{13}C NMR (100 MHz) spectrum of enoate **9c** in $CDCl_3$



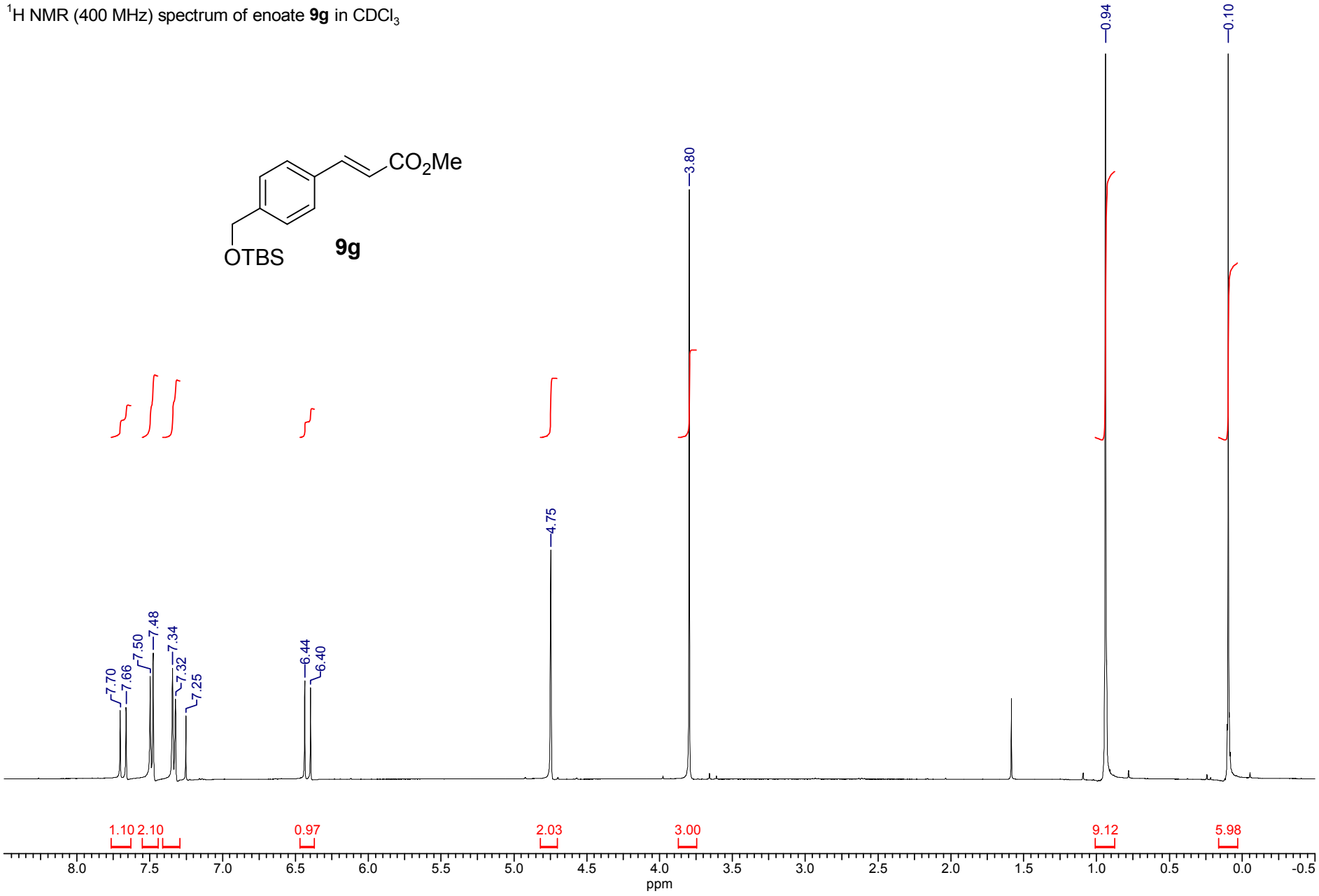
^{1}H NMR (400 MHz) spectrum of enoate **9d** in $CDCl_3$



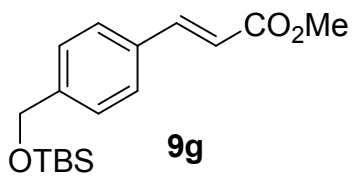
9d


^{13}C NMR (100 MHz) spectrum of enoate **9d** in $CDCl_3$
CO_2Me
F
9d
167.2
165.1
162.6
143.5
130.6
129.9
129.9
117.5
116.1
115.9
77.0
51.7
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

^{1}H NMR (400 MHz) spectrum of enoate **9g** in $CDCl_3$

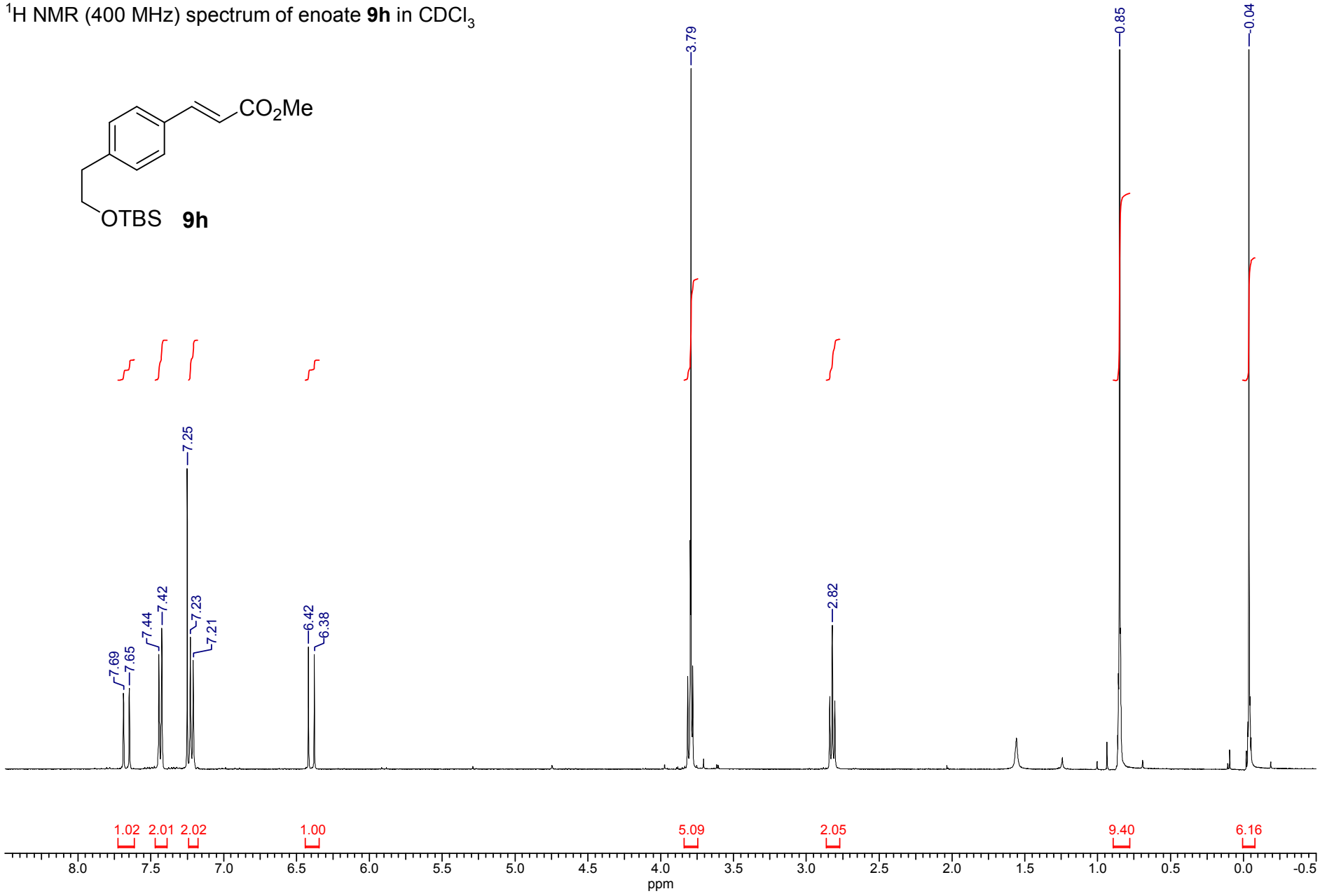


^{13}C NMR (100 MHz) spectrum of enoate **9g** in $CDCl_3$

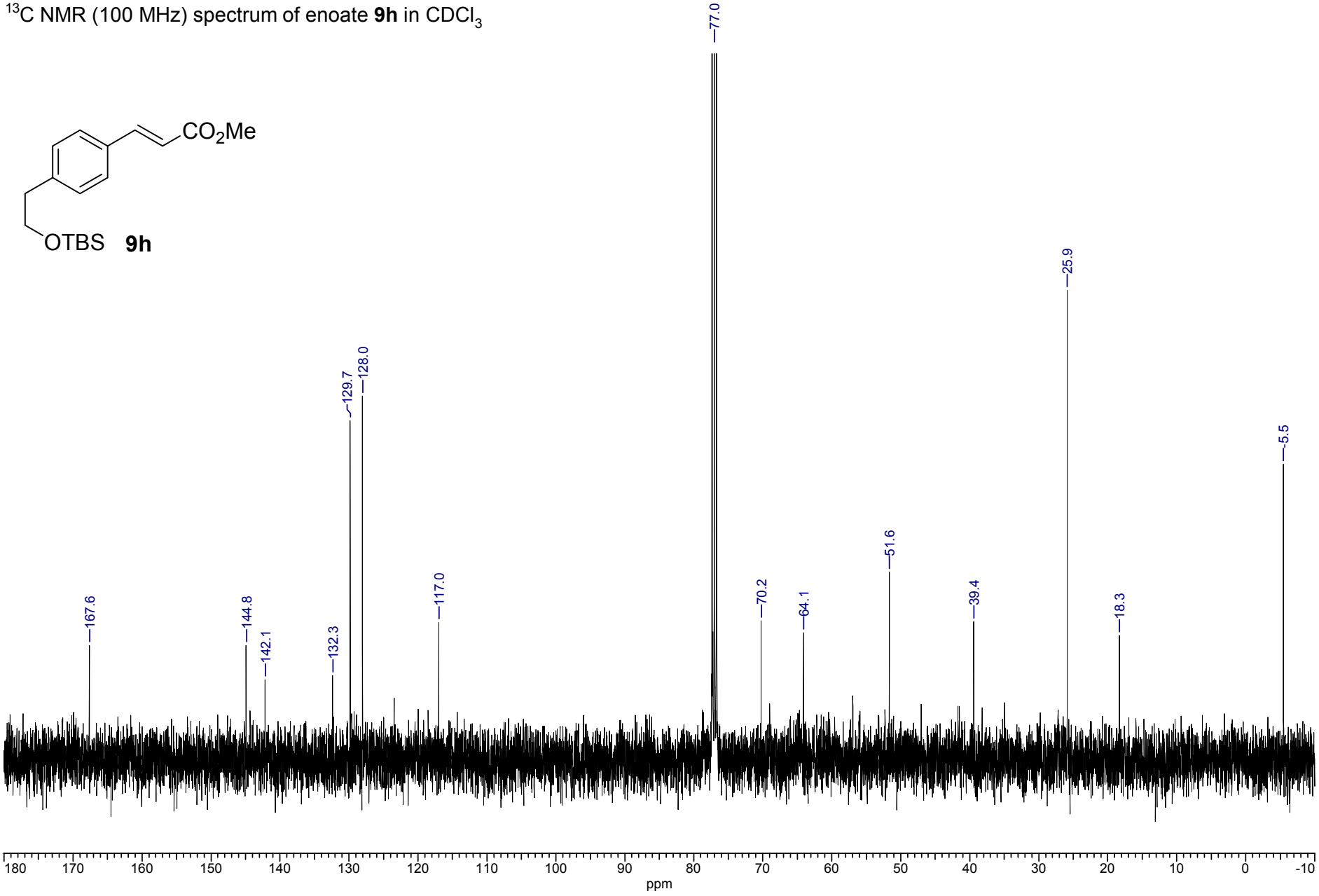


9g

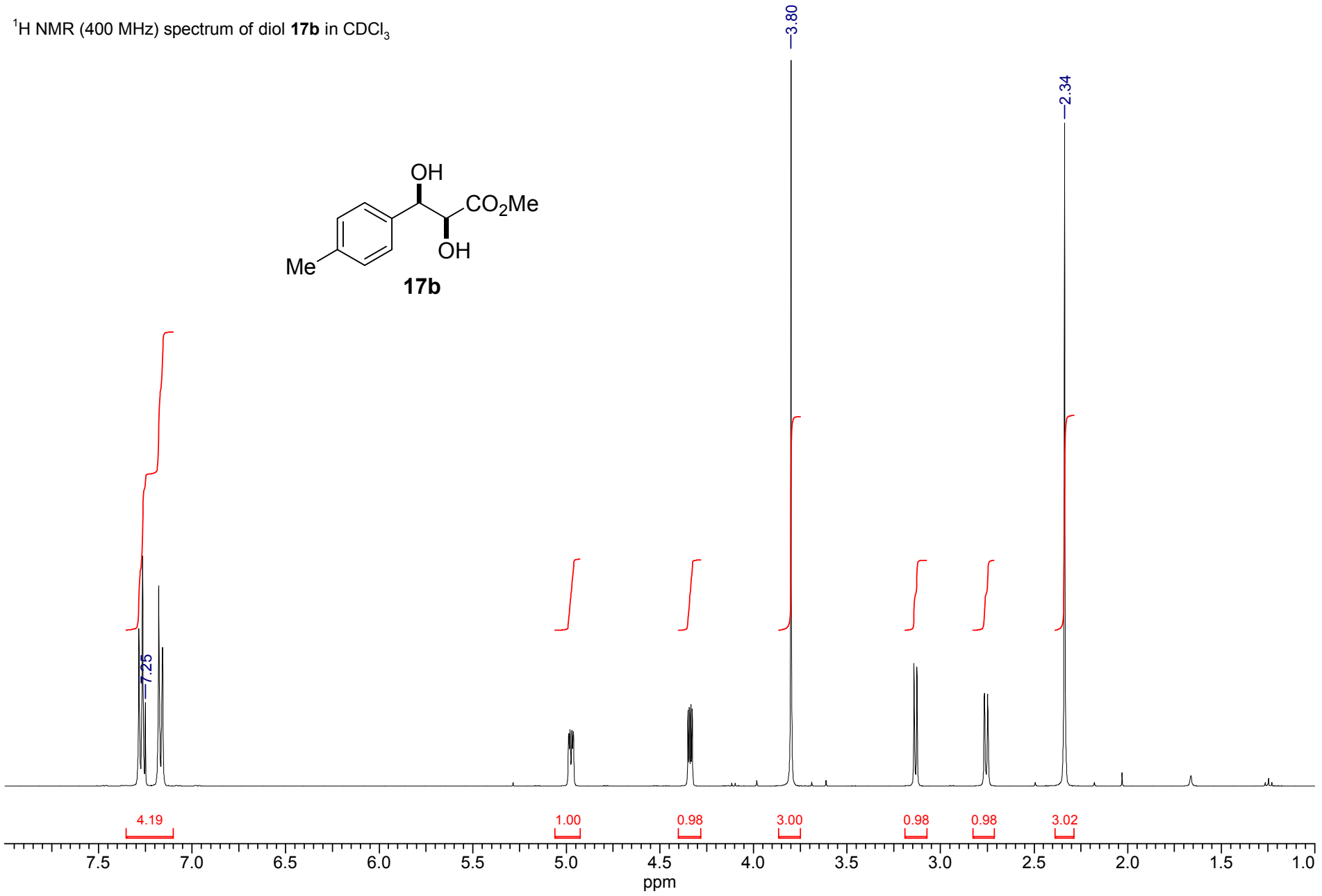
^{1}H NMR (400 MHz) spectrum of enoate **9h** in $CDCl_3$



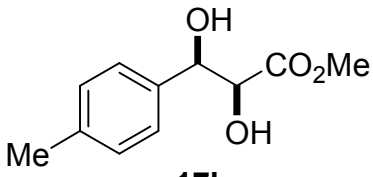
^{13}C NMR (100 MHz) spectrum of enoate **9h** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of diol **17b** in $CDCl_3$

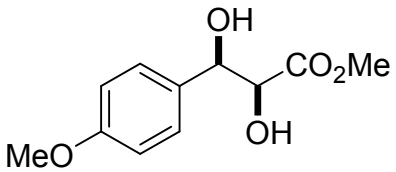


^{13}C NMR (100 MHz) spectrum of diol **17b** in $CDCl_3$



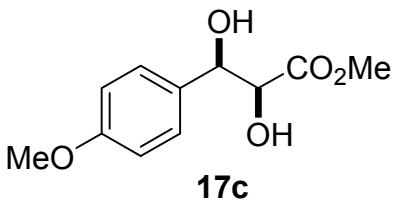
17b

^{1}H NMR (400 MHz) spectrum of diol **17c** in $CDCl_3$



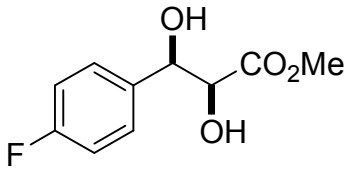
17c

^{13}C NMR (100 MHz) spectrum of diol **17c** in $CDCl_3$



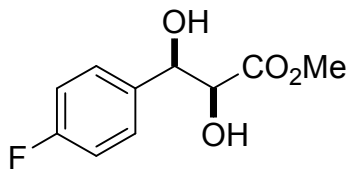
17c

^{1}H NMR (400 MHz) spectrum of diol **17d** in $CDCl_3$



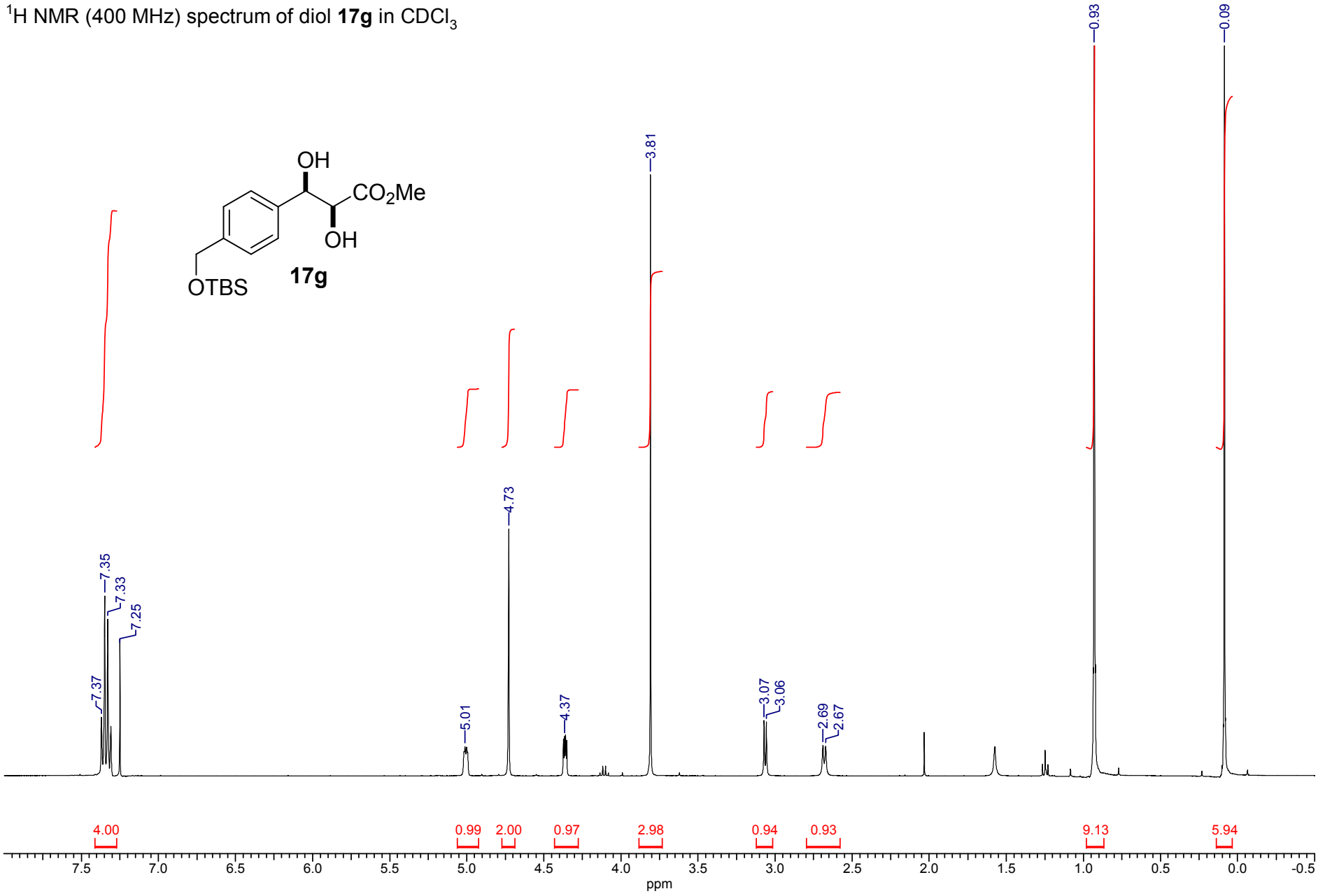
17d

^{13}C NMR (100 MHz) spectrum of diol **17d** in $CDCl_3$

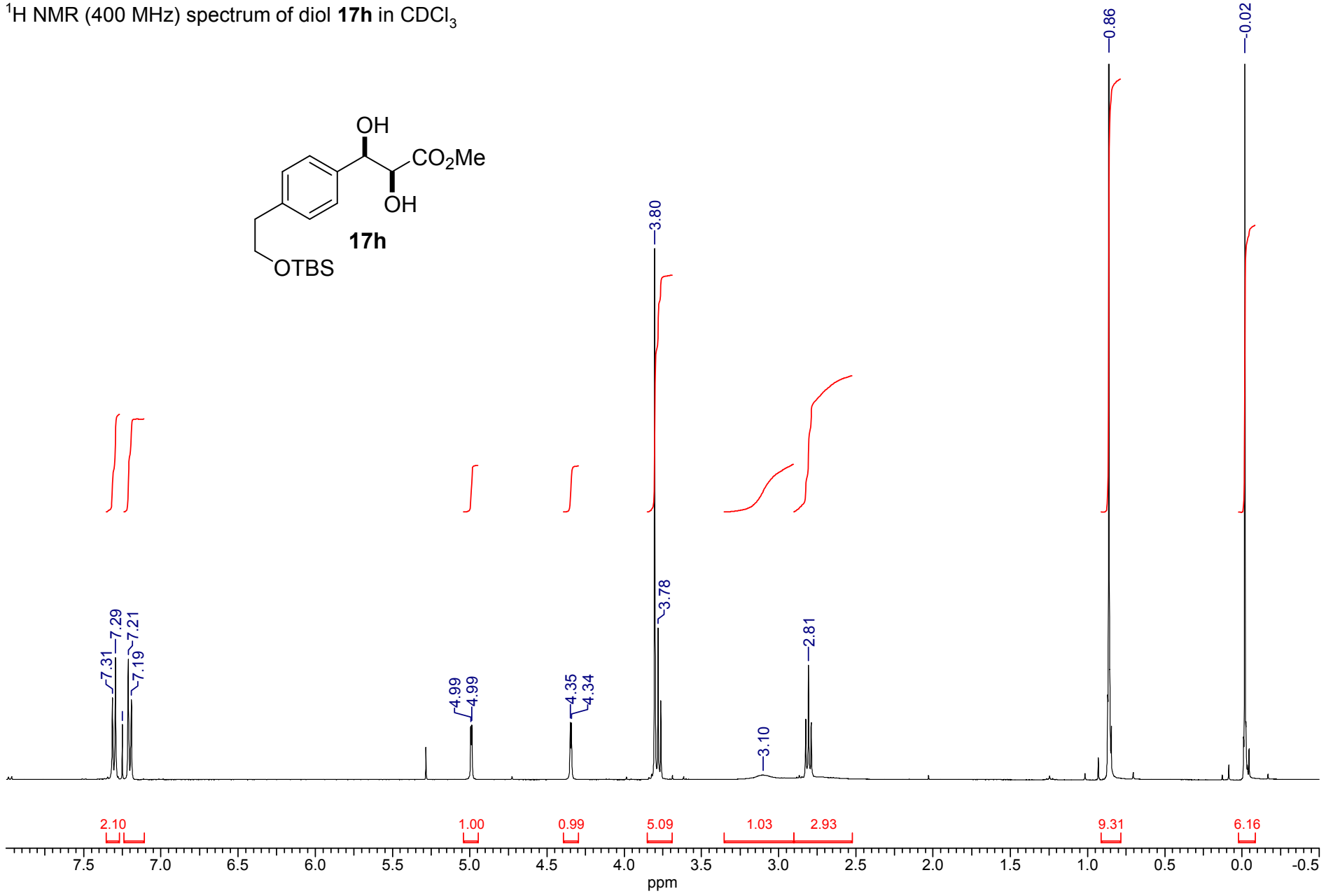


17d

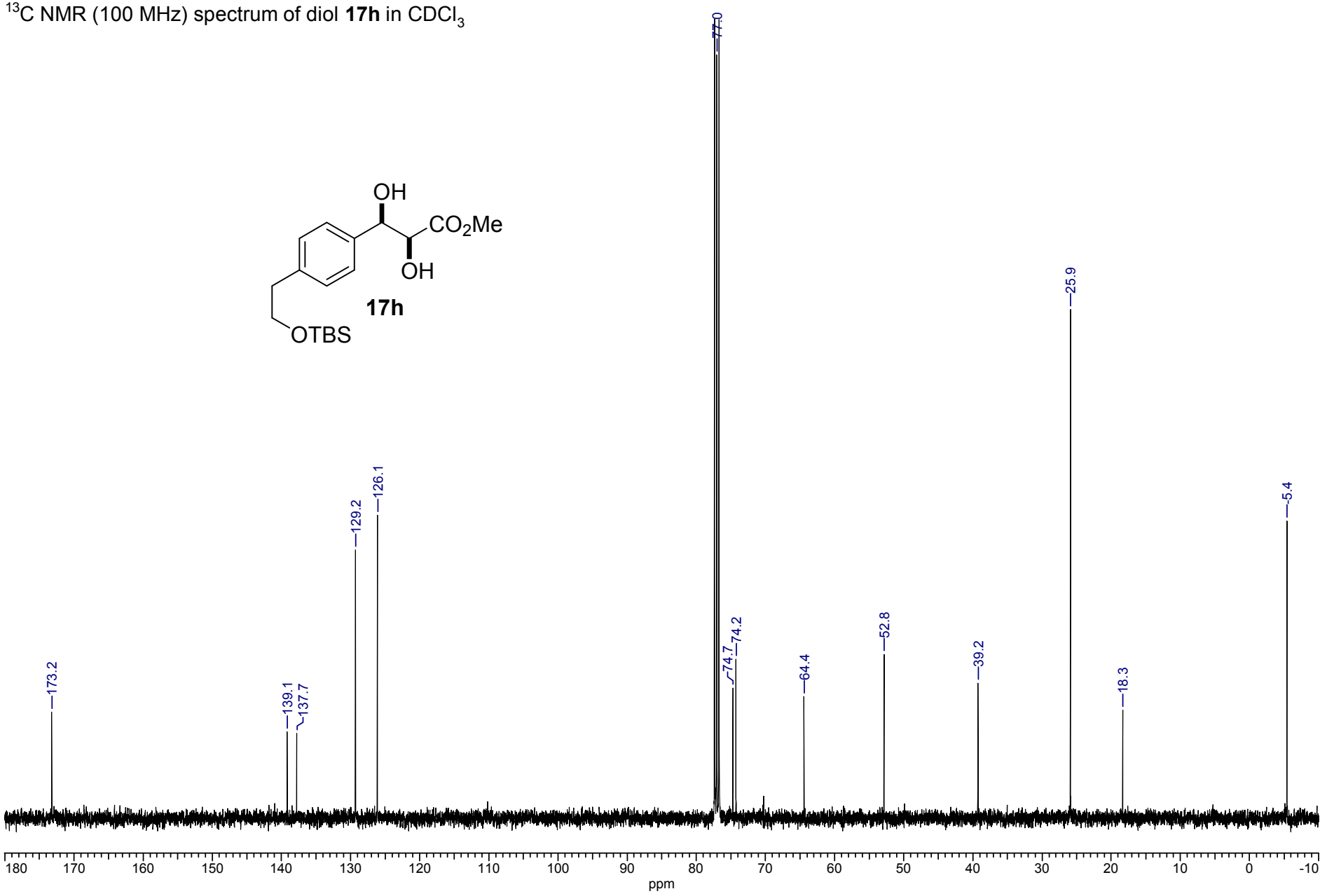
^{1}H NMR (400 MHz) spectrum of diol **17g** in $CDCl_3$



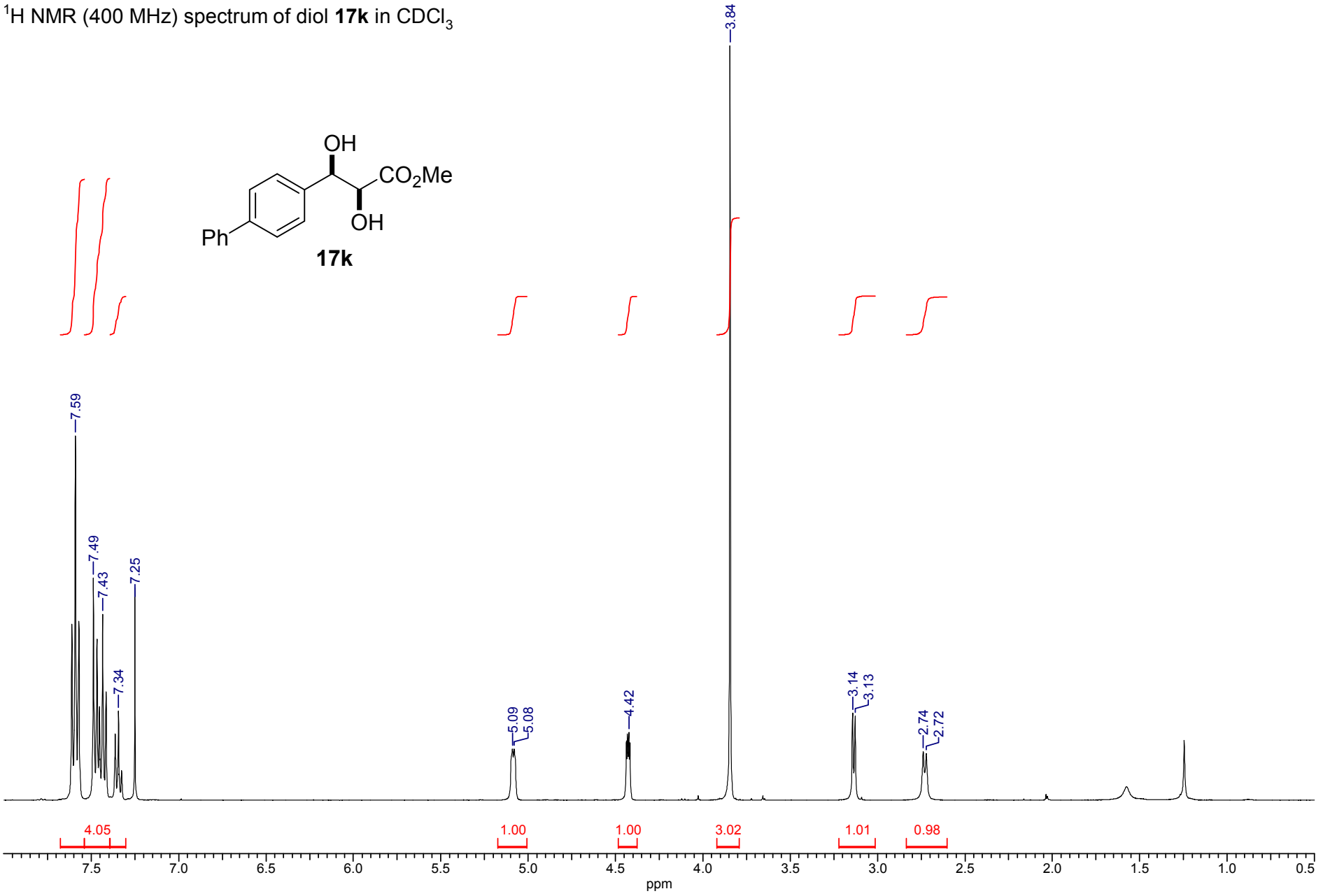
^{1}H NMR (400 MHz) spectrum of diol **17h** in $CDCl_3$



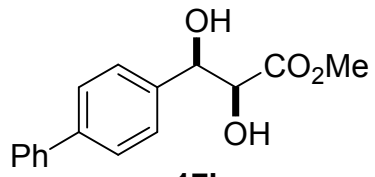
^{13}C NMR (100 MHz) spectrum of diol **17h** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of diol **17k** in $CDCl_3$

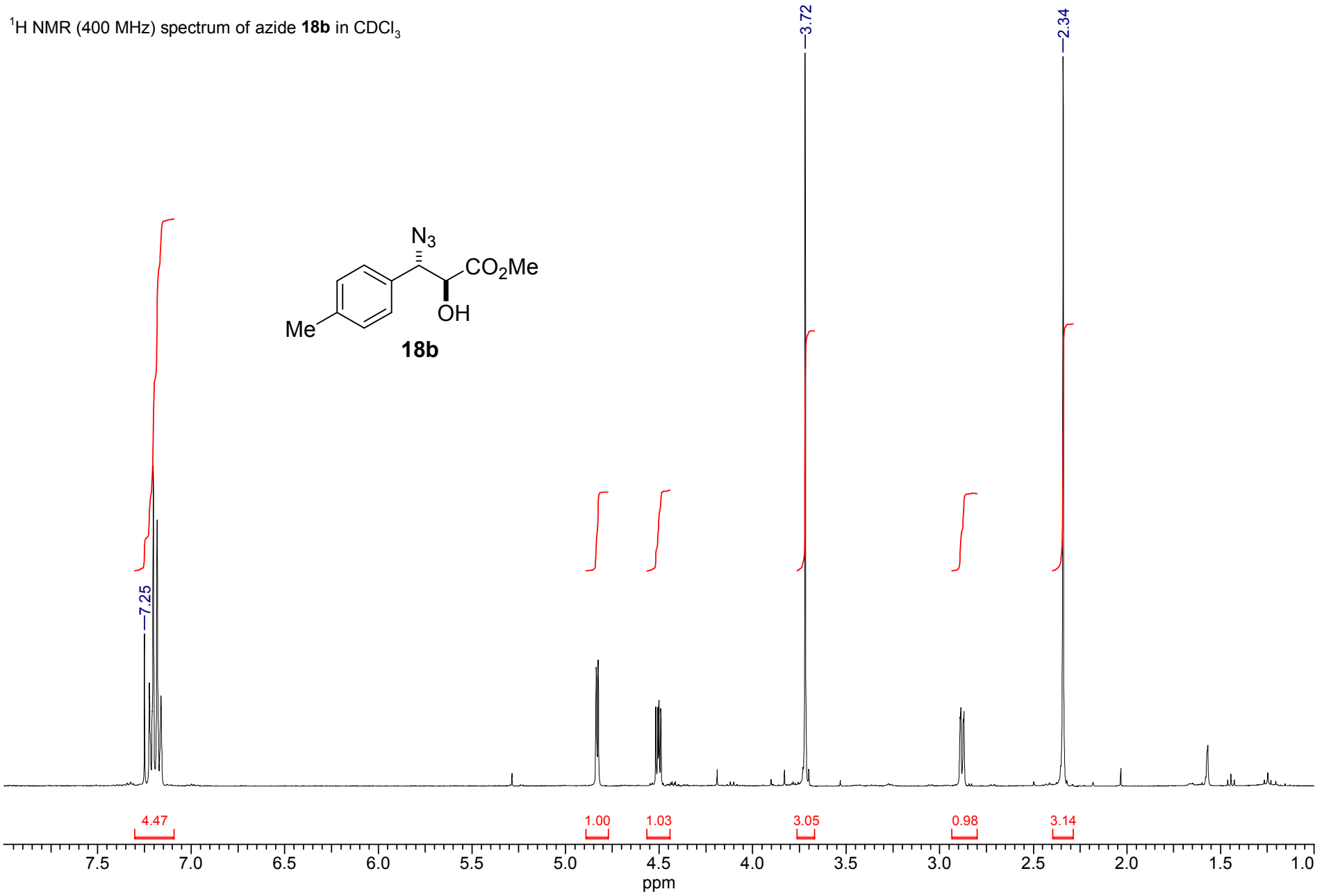


^{13}C NMR (100 MHz) spectrum of diol **17k** in $CDCl_3$

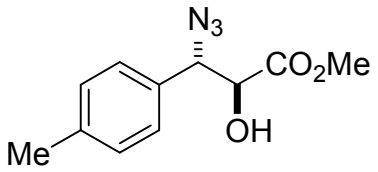


17k

^{1}H NMR (400 MHz) spectrum of azide **18b** in $CDCl_3$

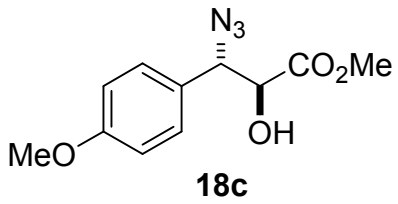


^{13}C NMR (100 MHz) spectrum of azide **18b** in $CDCl_3$



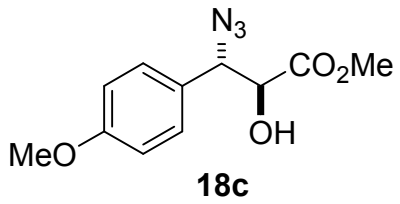
18b

^{1}H NMR (400 MHz) spectrum of azide **18c** in $CDCl_3$



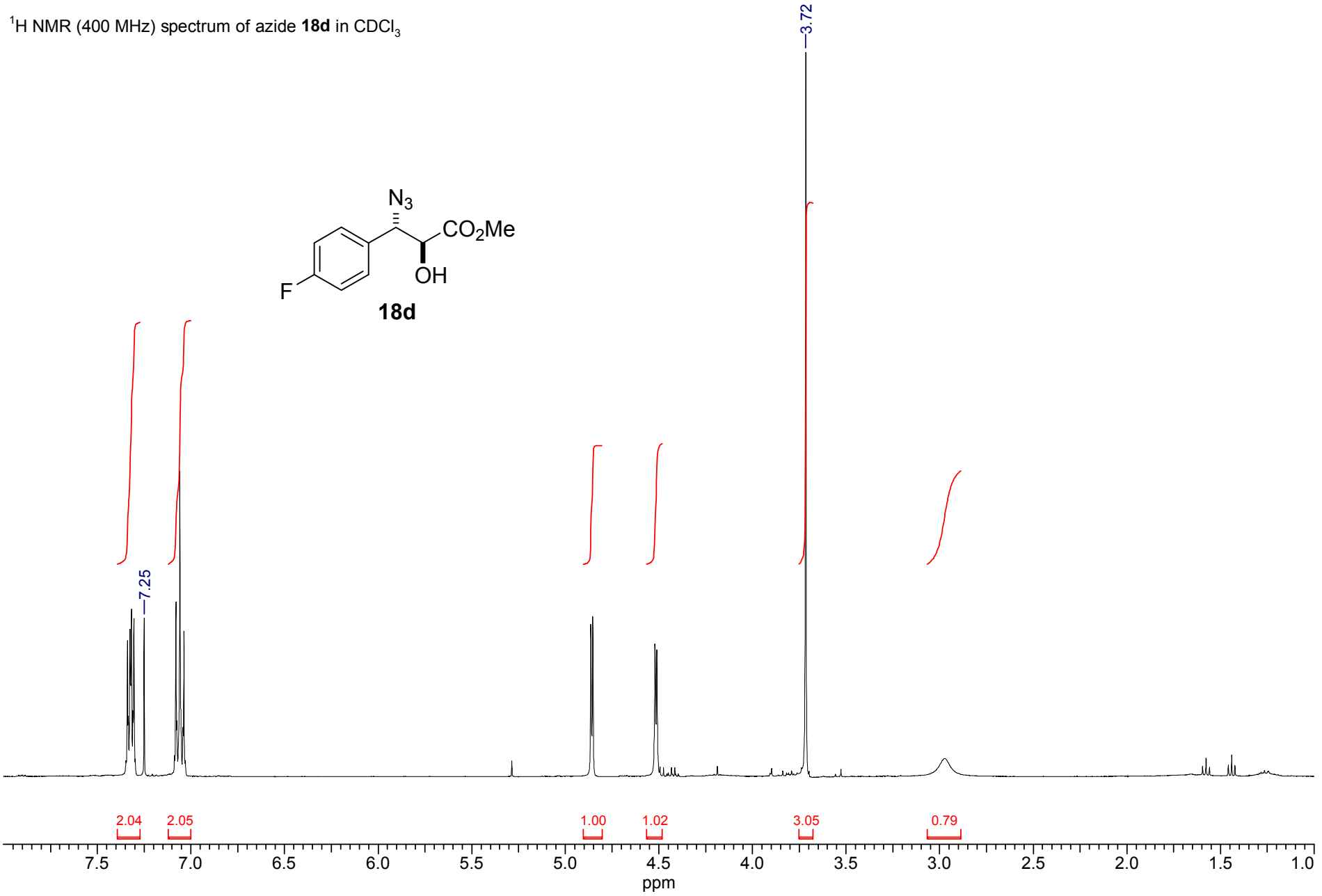
18c

^{13}C NMR (100 MHz) spectrum of azide **18c** in $CDCl_3$

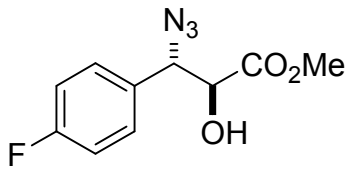


18c

^{1}H NMR (400 MHz) spectrum of azide **18d** in $CDCl_3$

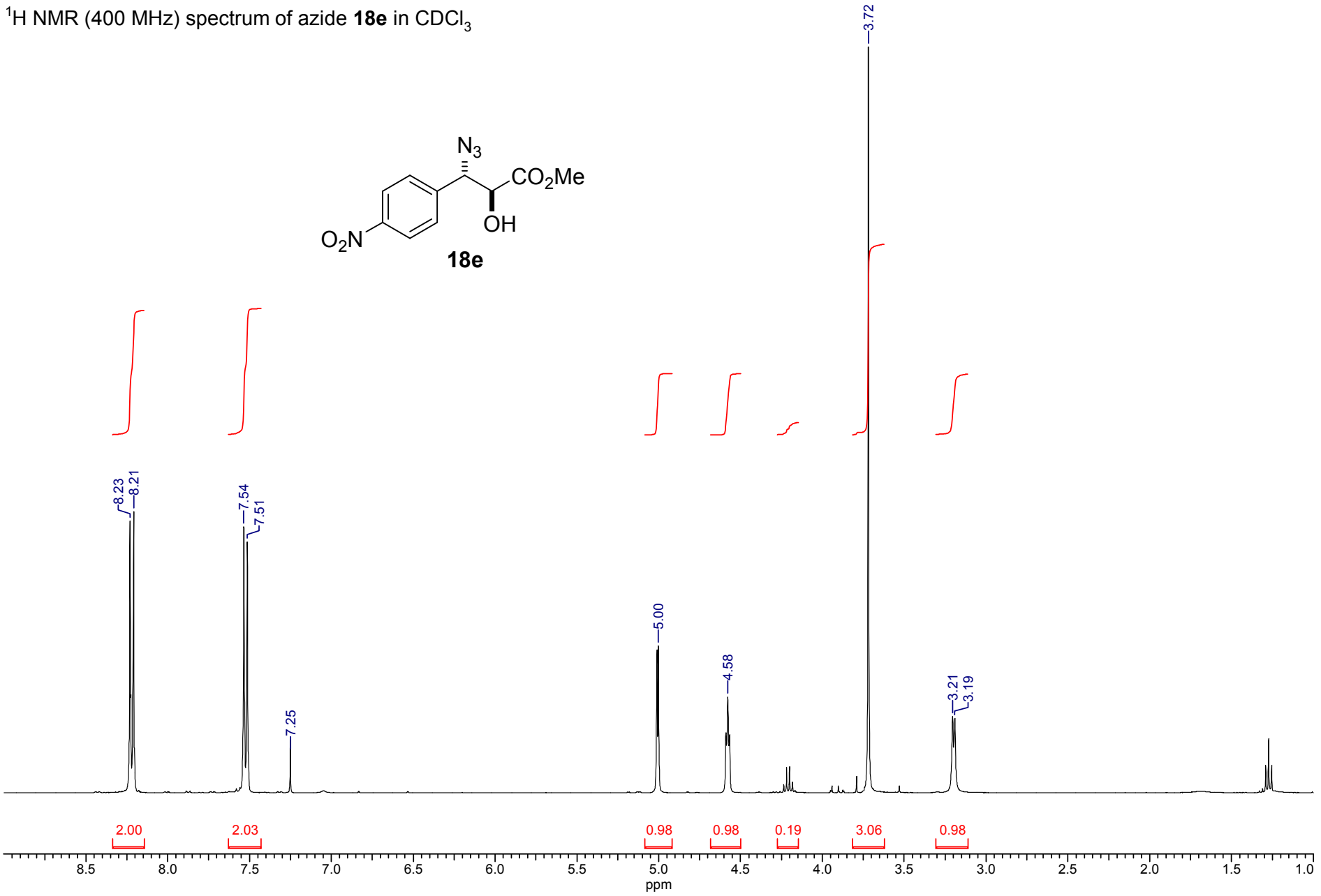


^{13}C NMR (100 MHz) spectrum of azide **18d** in $CDCl_3$

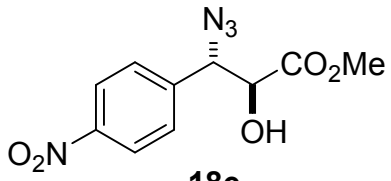


18d

^{1}H NMR (400 MHz) spectrum of azide **18e** in $CDCl_3$

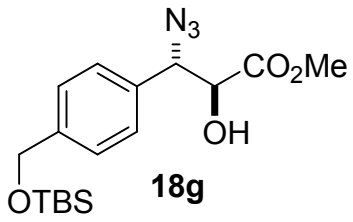


^{13}C NMR (100 MHz) spectrum of azide **18e** in $CDCl_3$



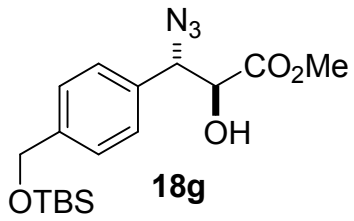
18e

^{1}H NMR (400 MHz) spectrum of azide **18g** in $CDCl_3$



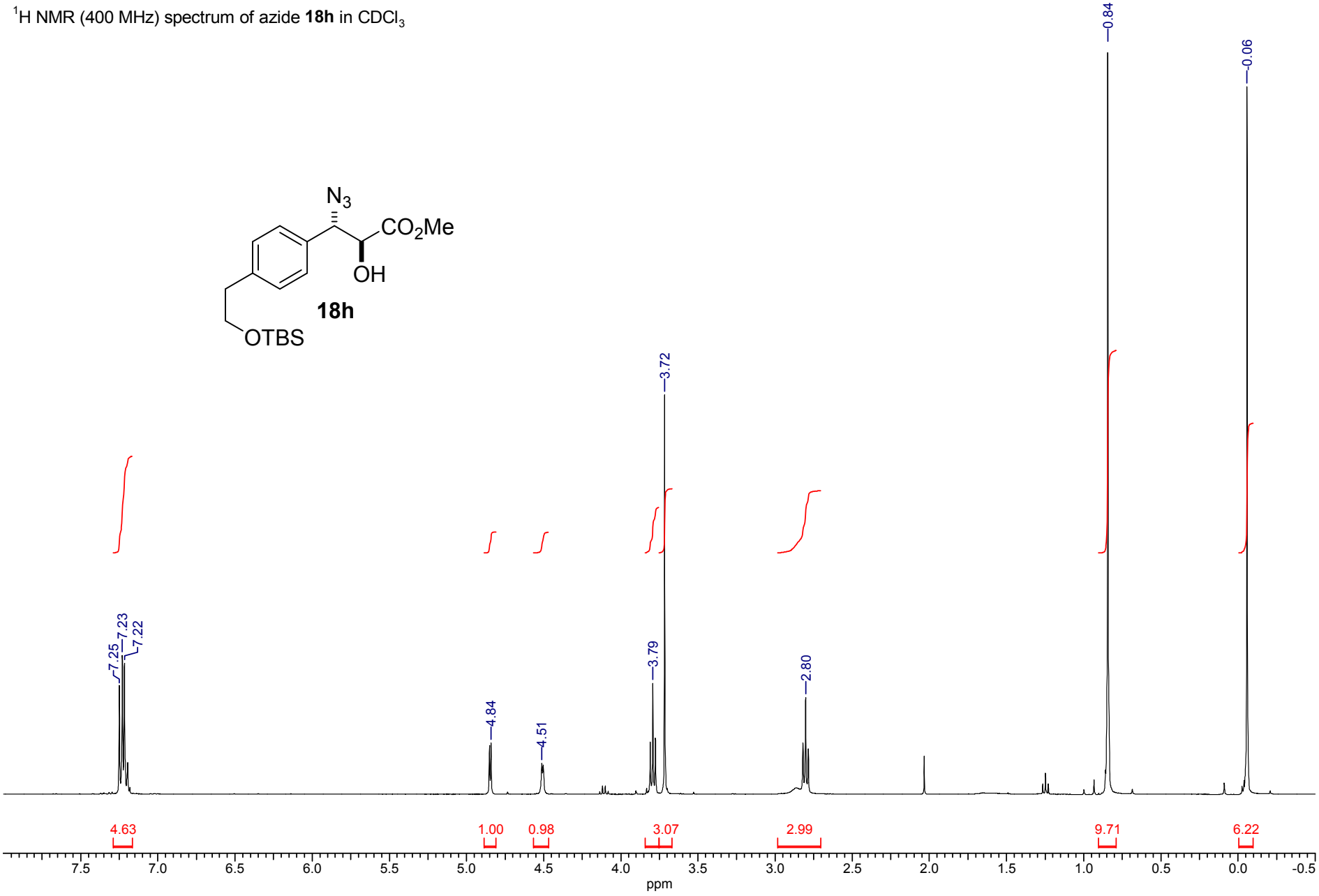
18g

^{13}C NMR (100 MHz) spectrum of azide **18g** in $CDCl_3$

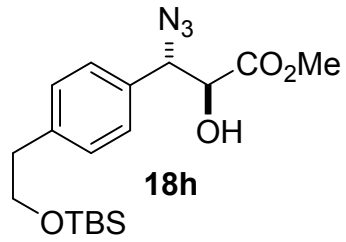


18g

^{1}H NMR (400 MHz) spectrum of azide **18h** in $CDCl_3$

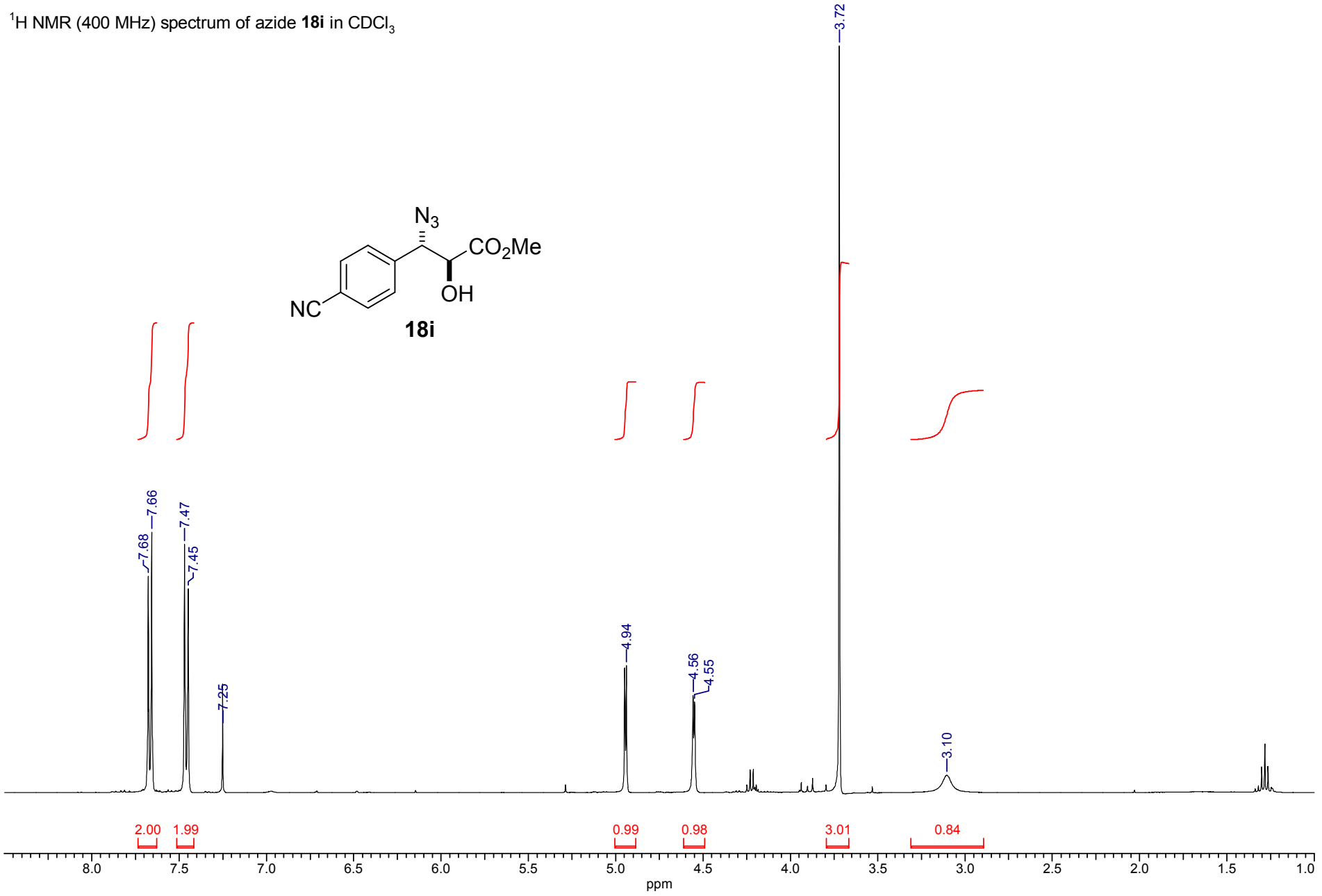


^{13}C NMR (100 MHz) spectrum of azide **18h** in $CDCl_3$

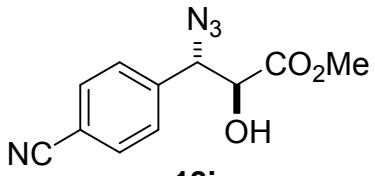


18h

^{1}H NMR (400 MHz) spectrum of azide **18i** in $CDCl_3$

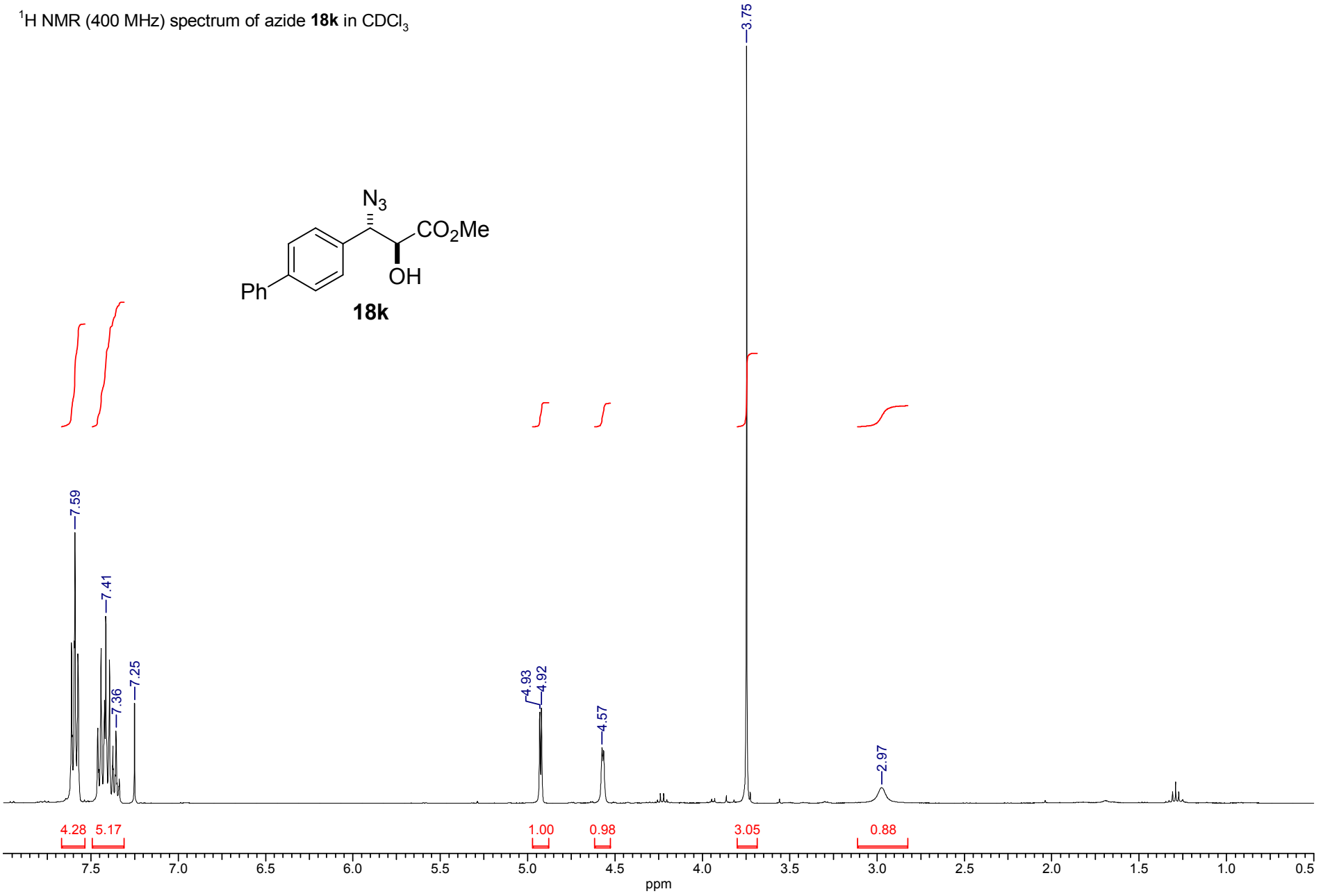


^{13}C NMR (100 MHz) spectrum of azide **18i** in $CDCl_3$

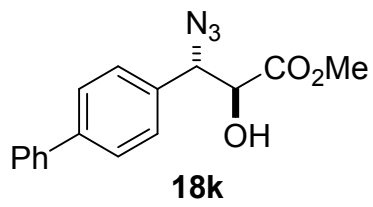


18i

^{1}H NMR (400 MHz) spectrum of azide **18k** in $CDCl_3$

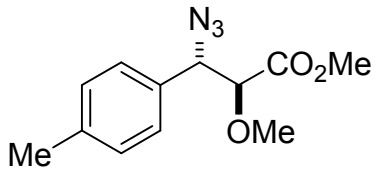


^{13}C NMR (100 MHz) spectrum of azide **18k** in $CDCl_3$



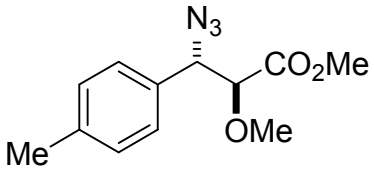
18k

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19b** in $CDCl_3$



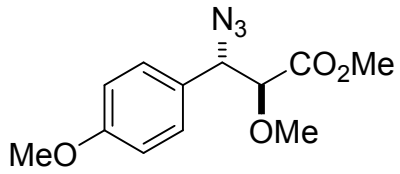
19b

^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19b** in $CDCl_3$



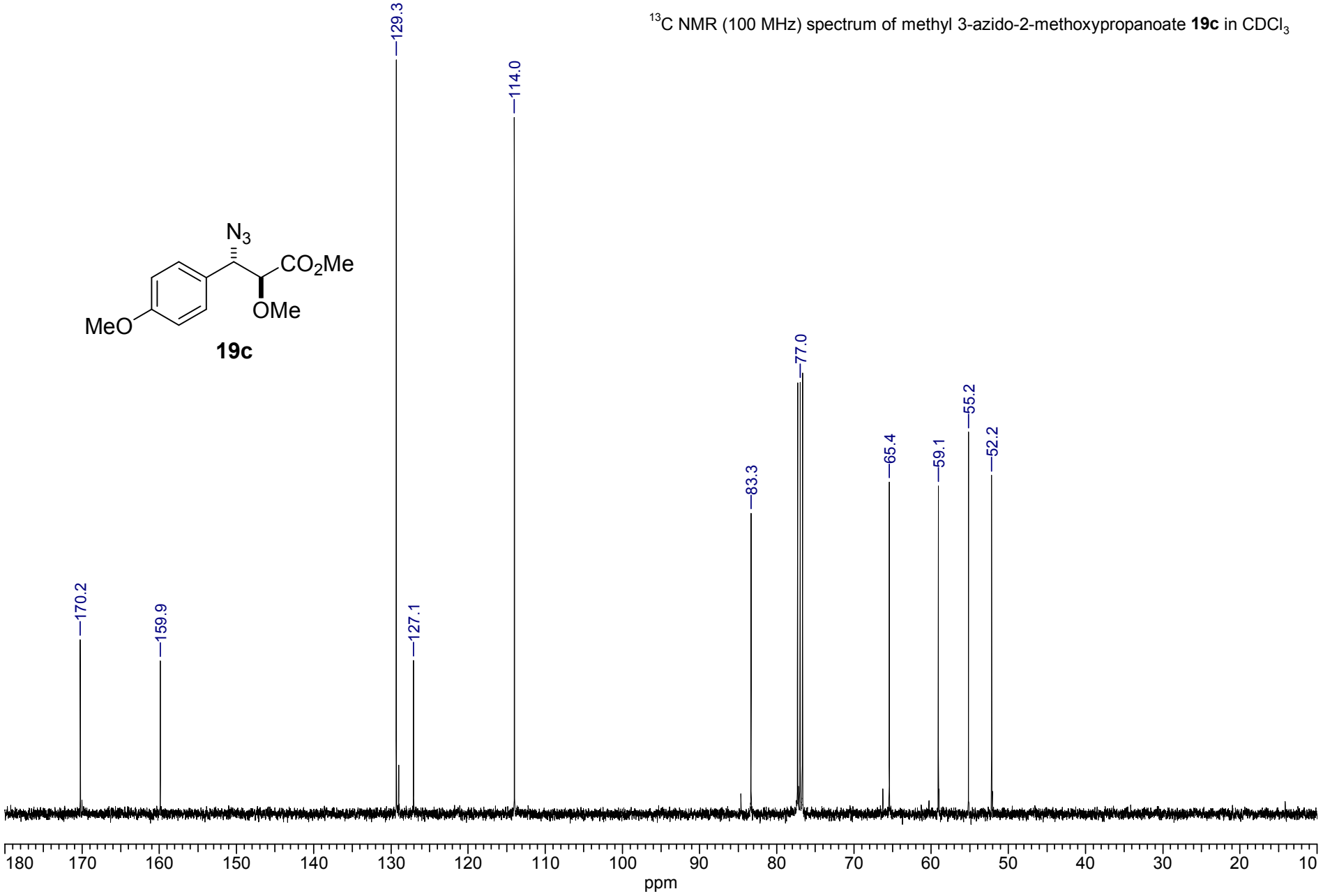
19b

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19c** in $CDCl_3$

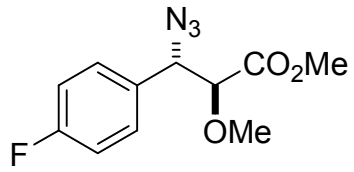


19c

^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19c** in $CDCl_3$

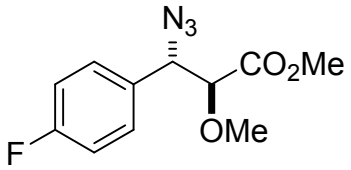


^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19d** in $CDCl_3$



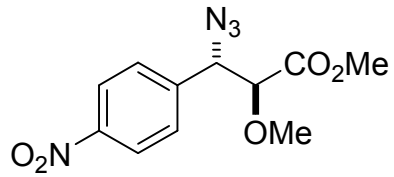
19d

^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19d** in $CDCl_3$



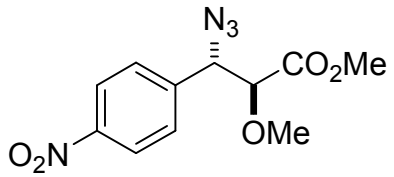
19d

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19e** in $CDCl_3$



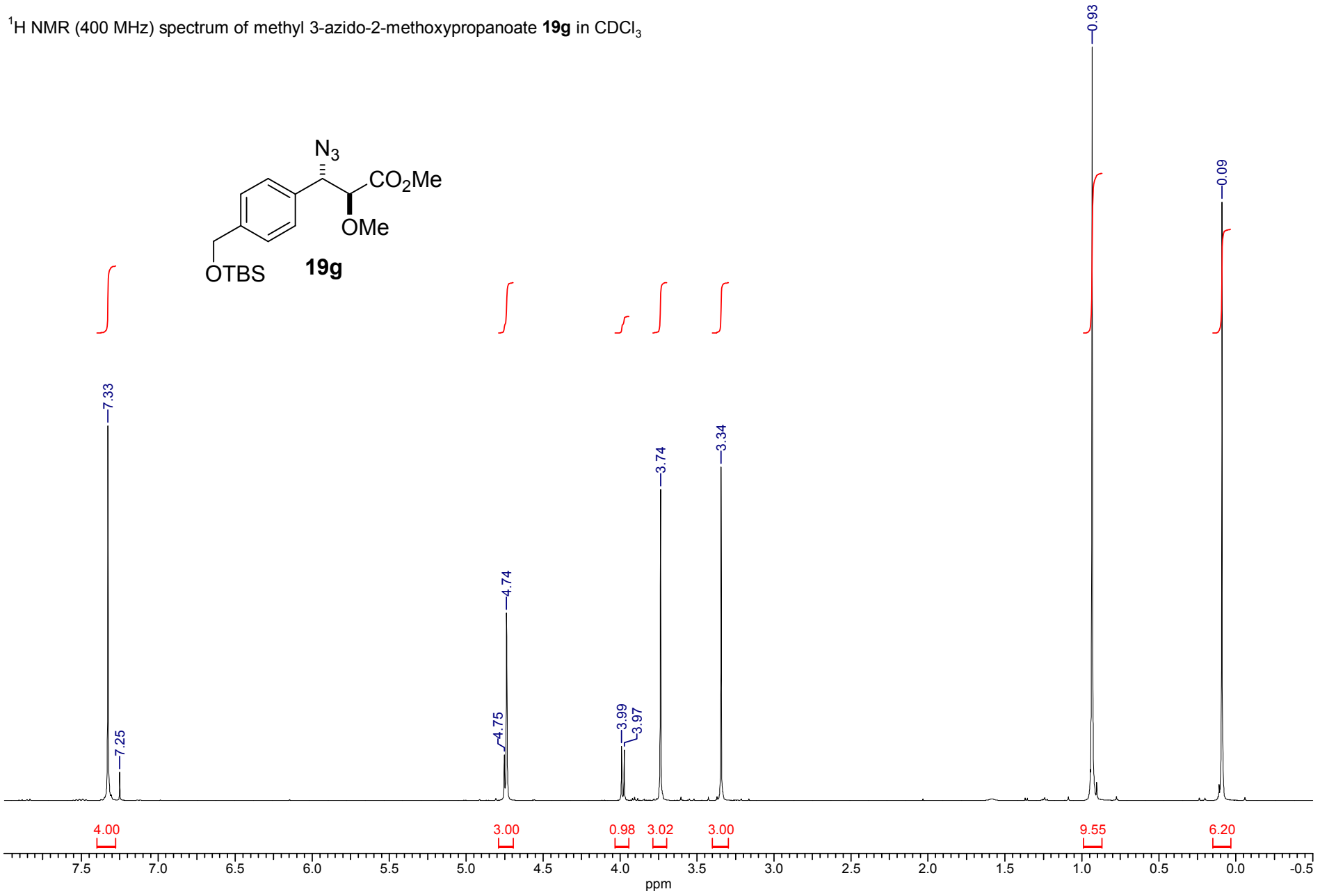
19e

^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19e** in $CDCl_3$

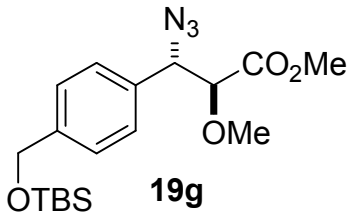


19e

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19g** in $CDCl_3$

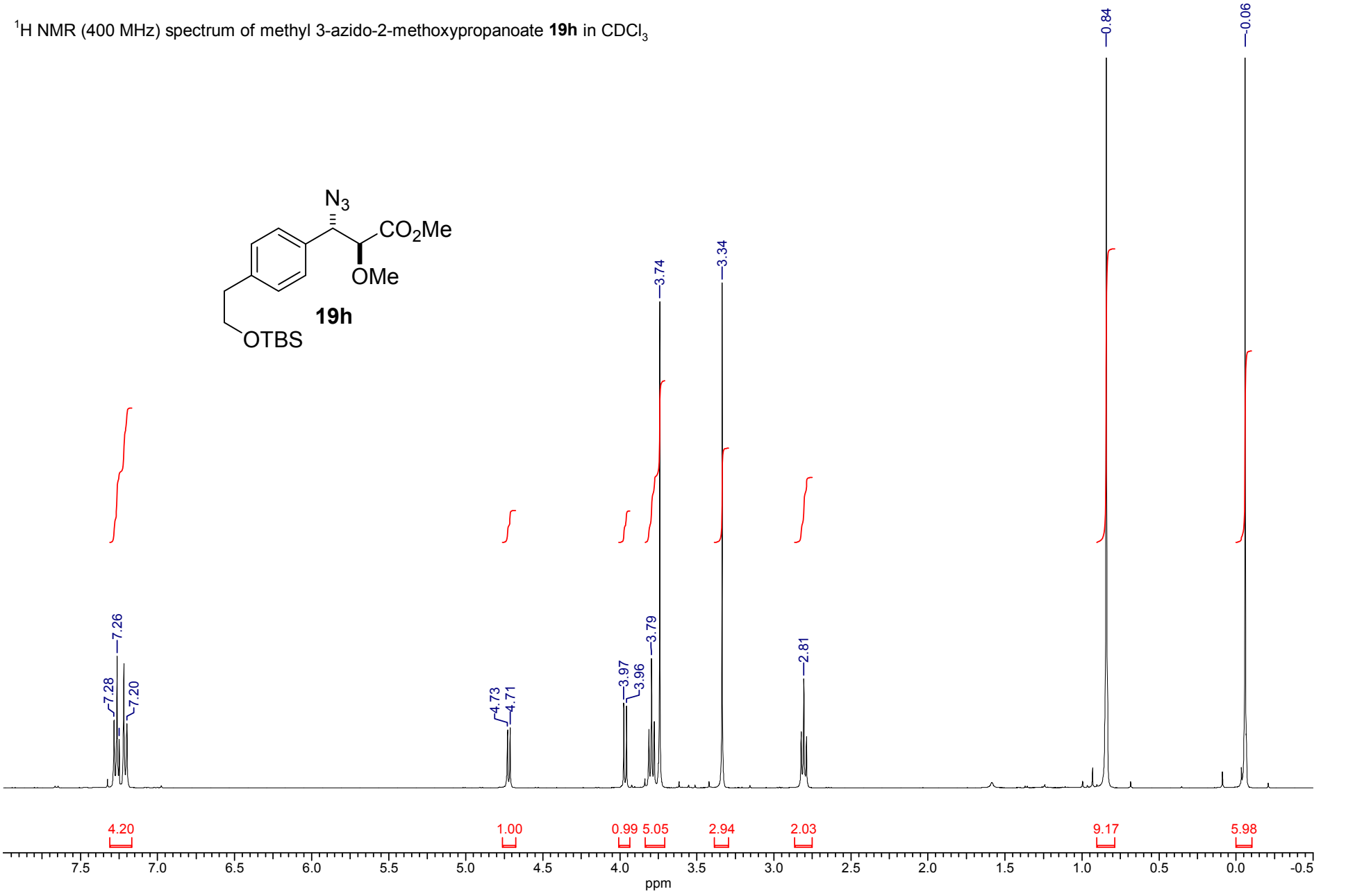


^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19g** in $CDCl_3$

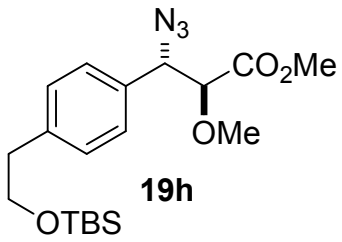


19g

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19h** in $CDCl_3$

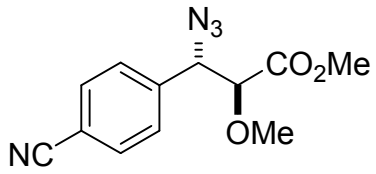


^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19h** in $CDCl_3$



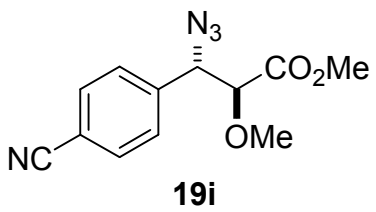
19h

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19i** in $CDCl_3$



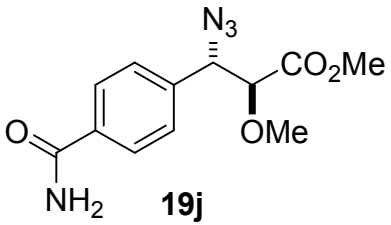
19i

^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19i** in $CDCl_3$



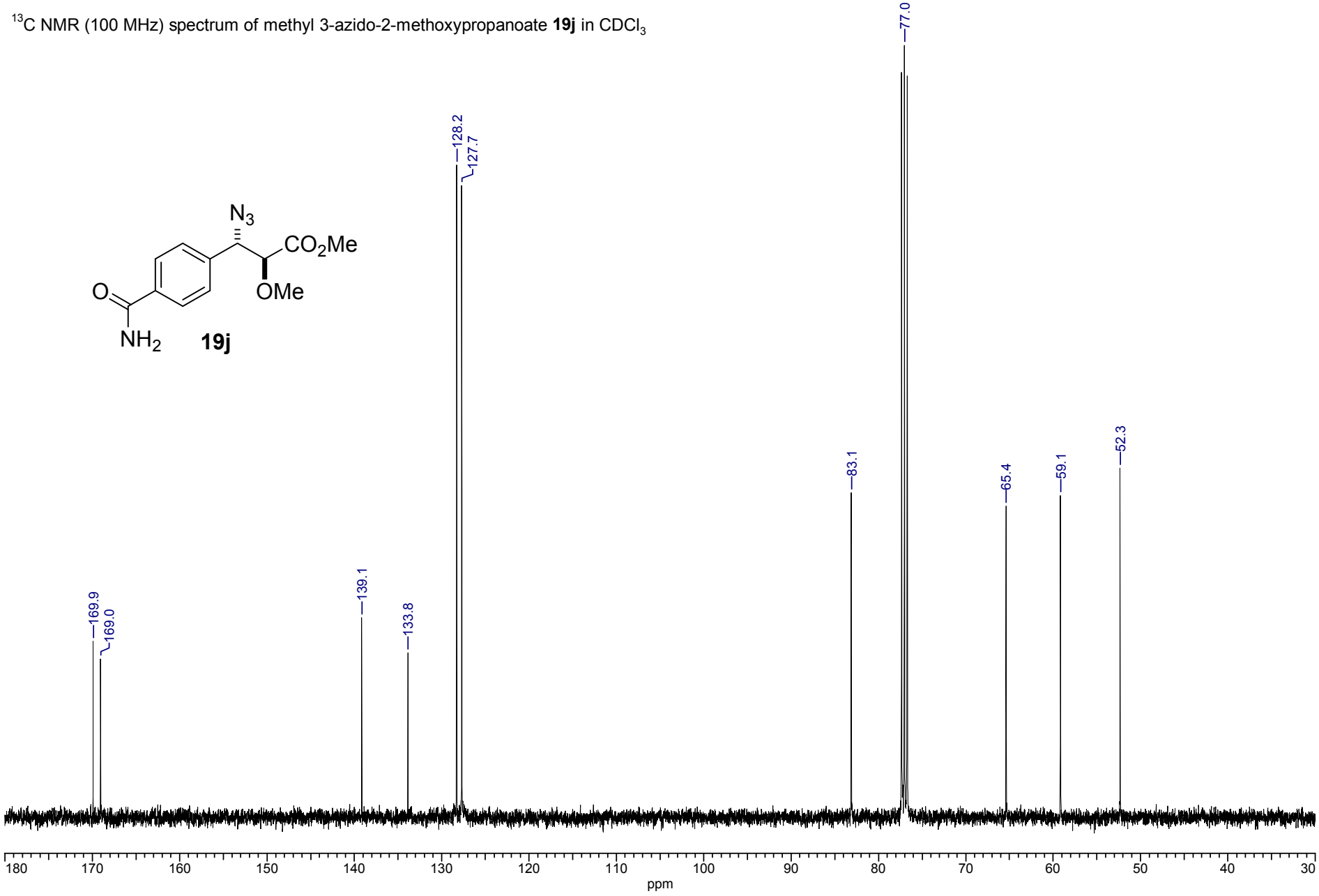
19i

^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19j** in $CDCl_3$

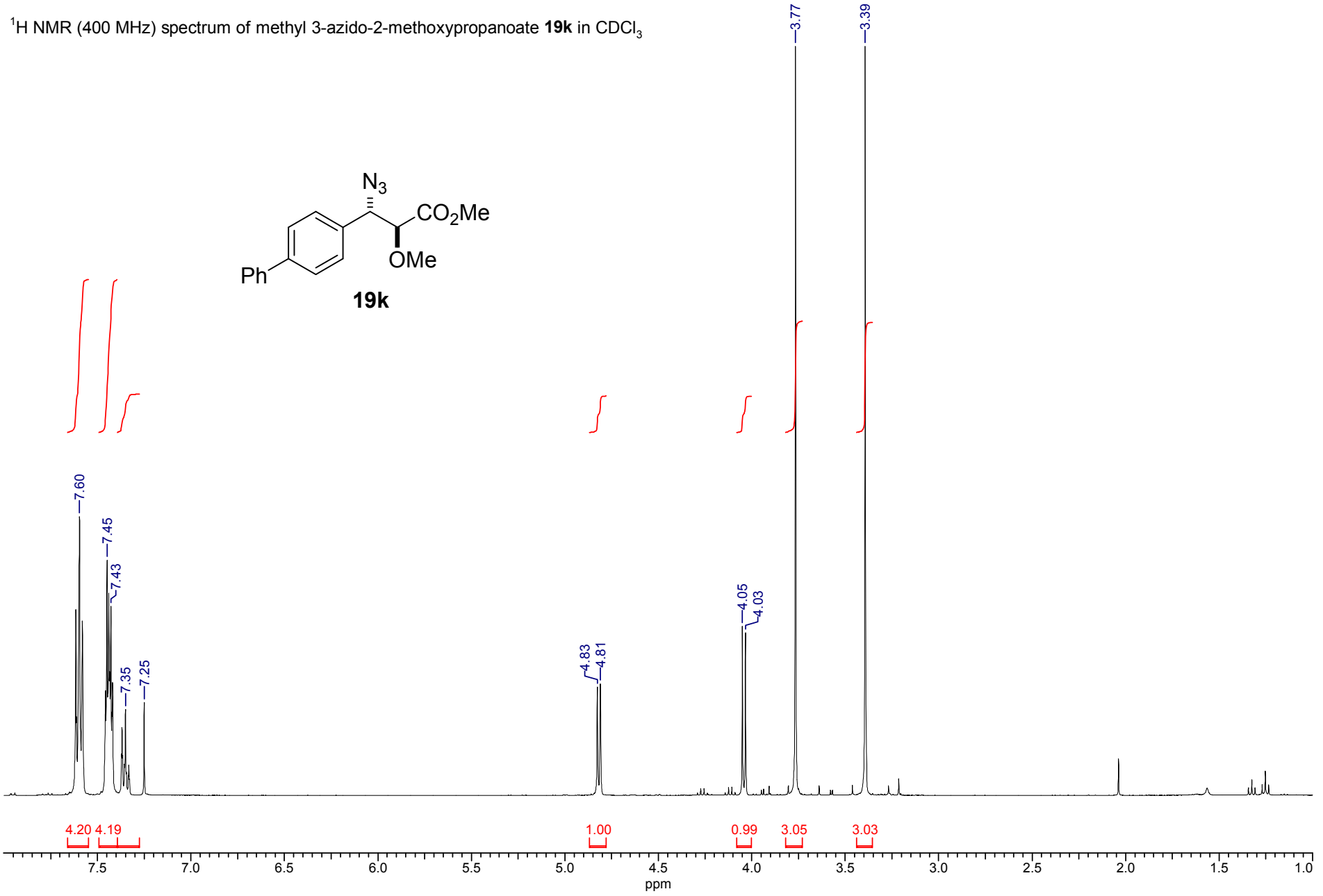


19j

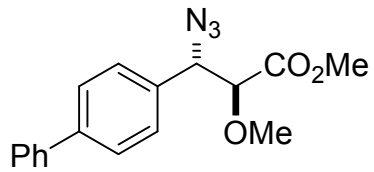
^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19j** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19k** in $CDCl_3$

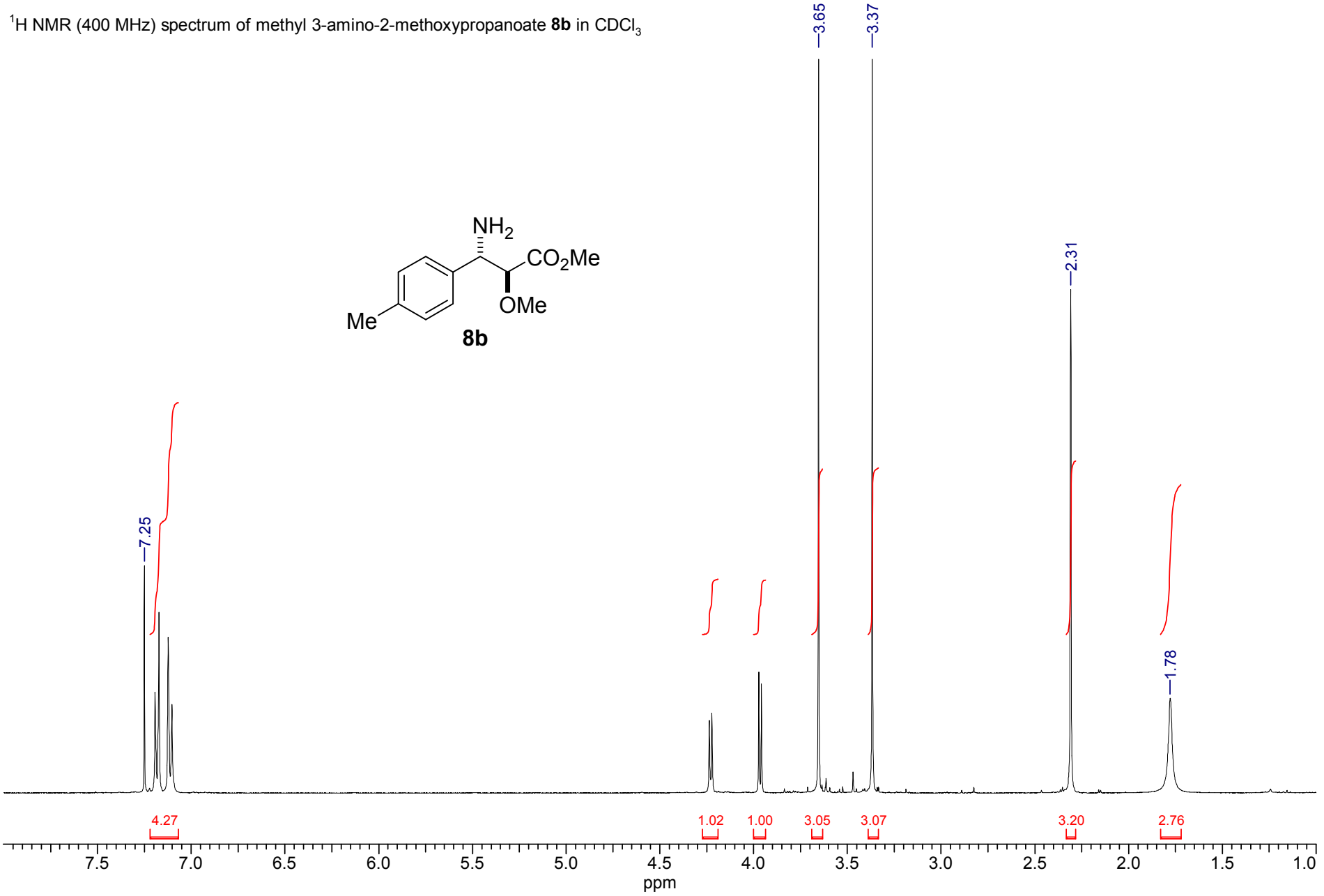


^{13}C NMR (100 MHz) spectrum of methyl 3-azido-2-methoxypropanoate **19k** in $CDCl_3$

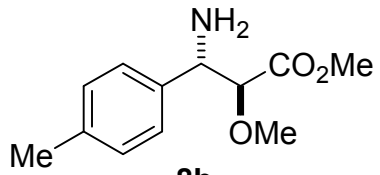


19k

^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8b** in $CDCl_3$

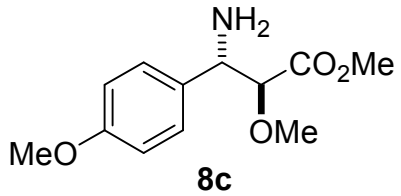


^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8b** in $CDCl_3$



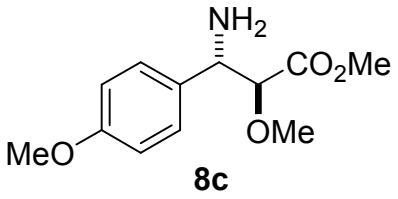
8b

^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8c** in $CDCl_3$



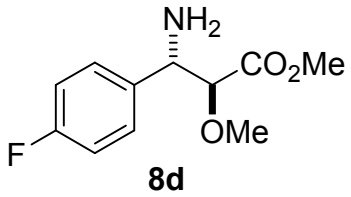
8c

^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8c** in $CDCl_3$



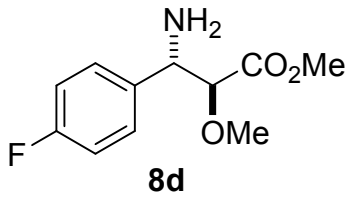
8c

^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8d** in $CDCl_3$



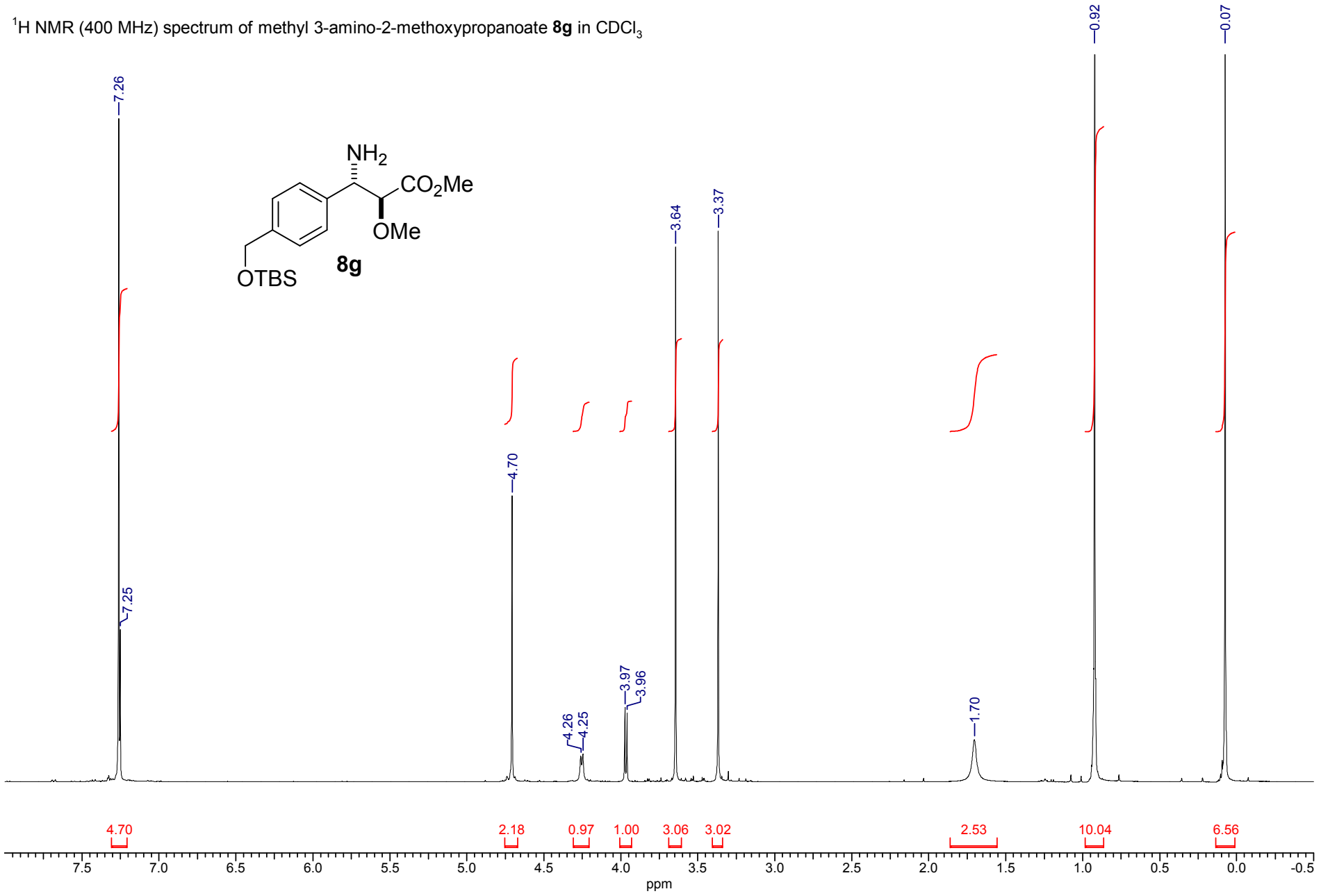
8d

^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8d** in $CDCl_3$

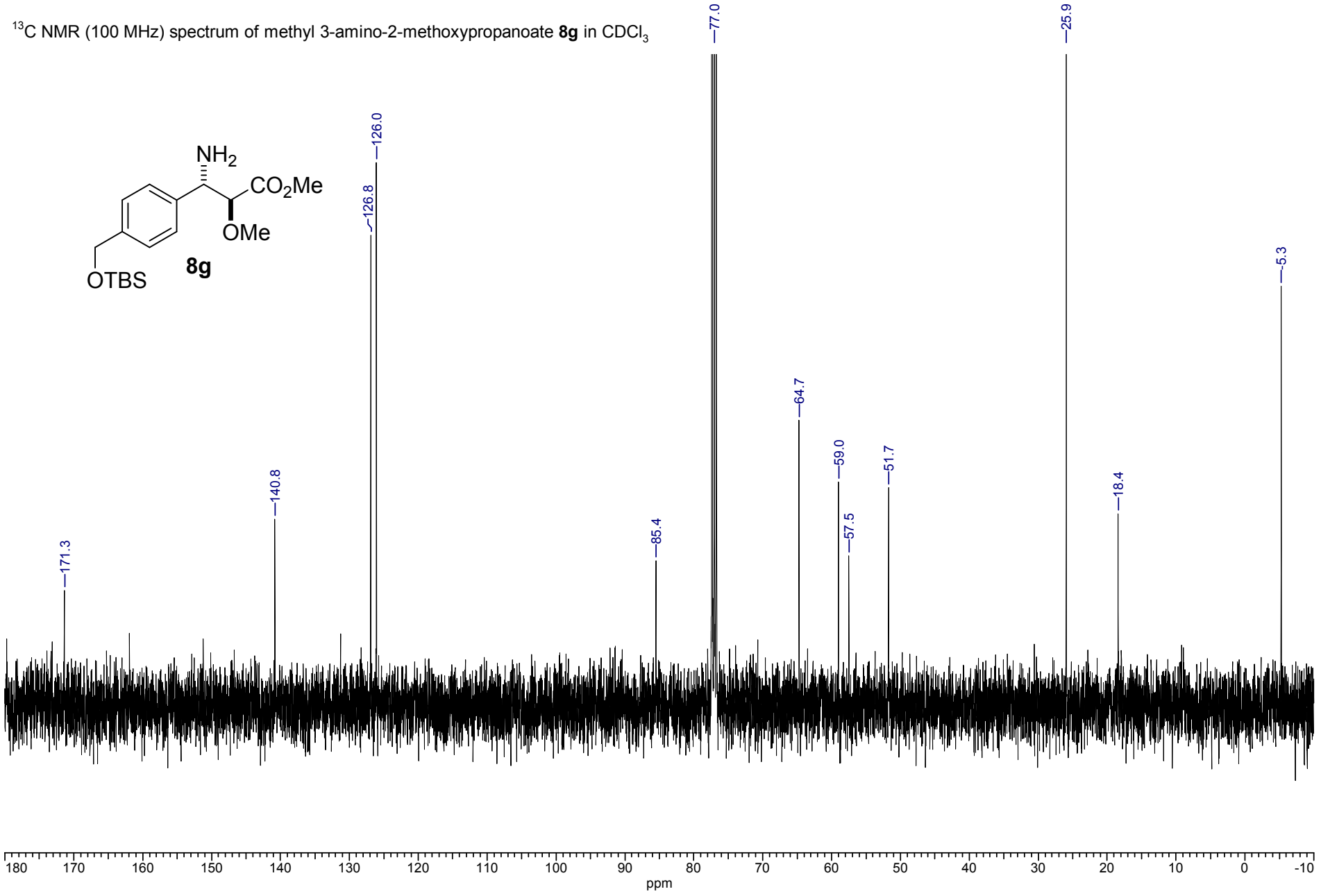


8d

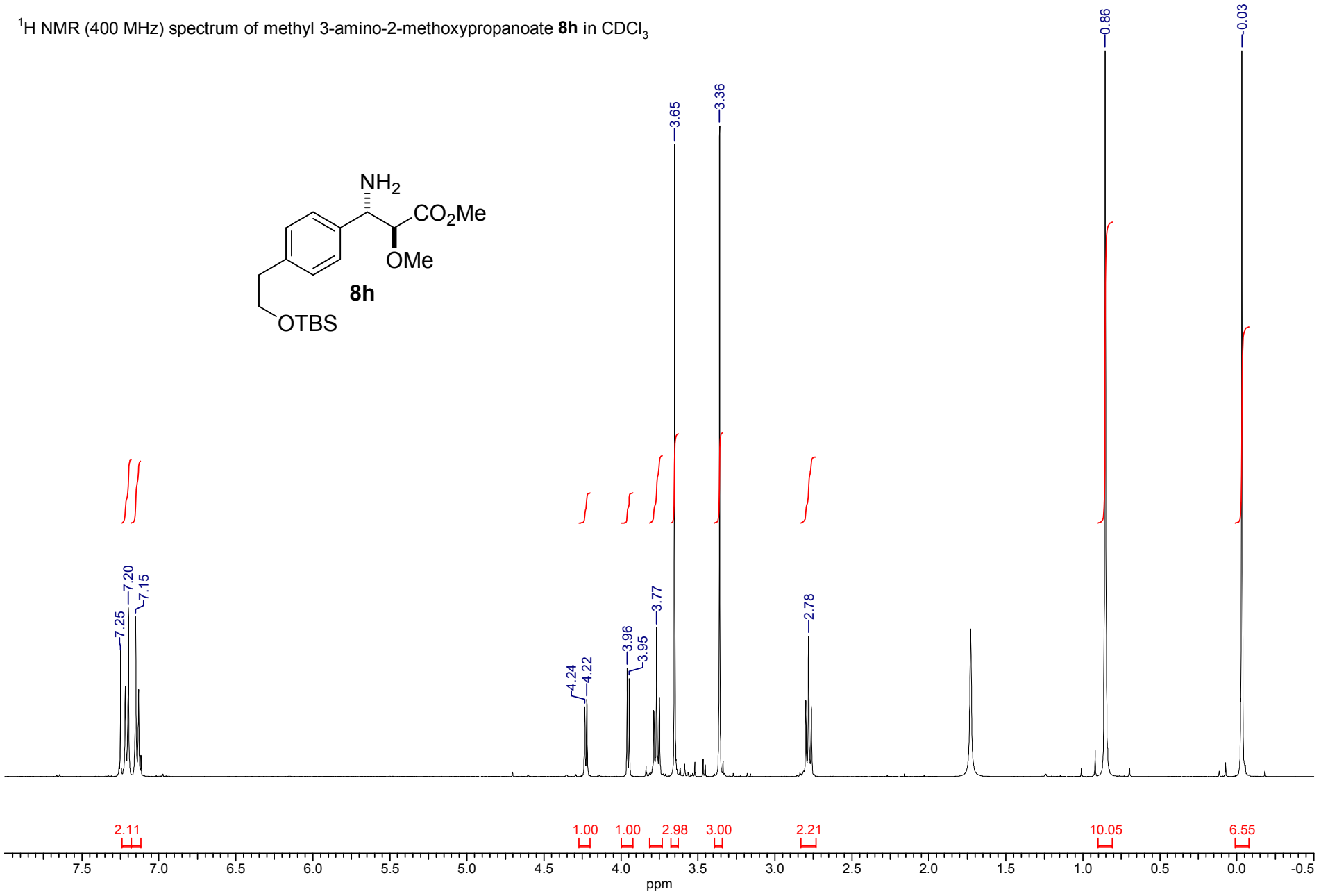
^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8g** in $CDCl_3$



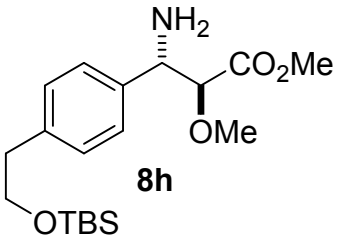
^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8g** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8h** in $CDCl_3$

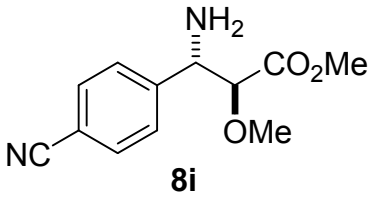


^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8h** in $CDCl_3$



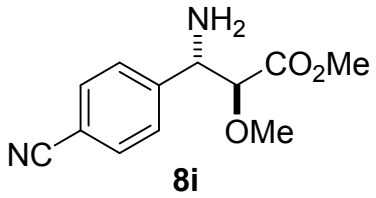
8h

^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8i** in $CDCl_3$



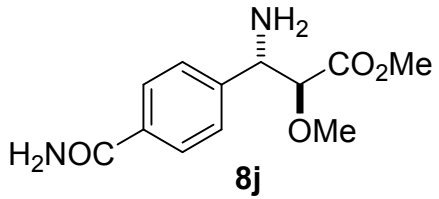
8i

^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8i** in $CDCl_3$



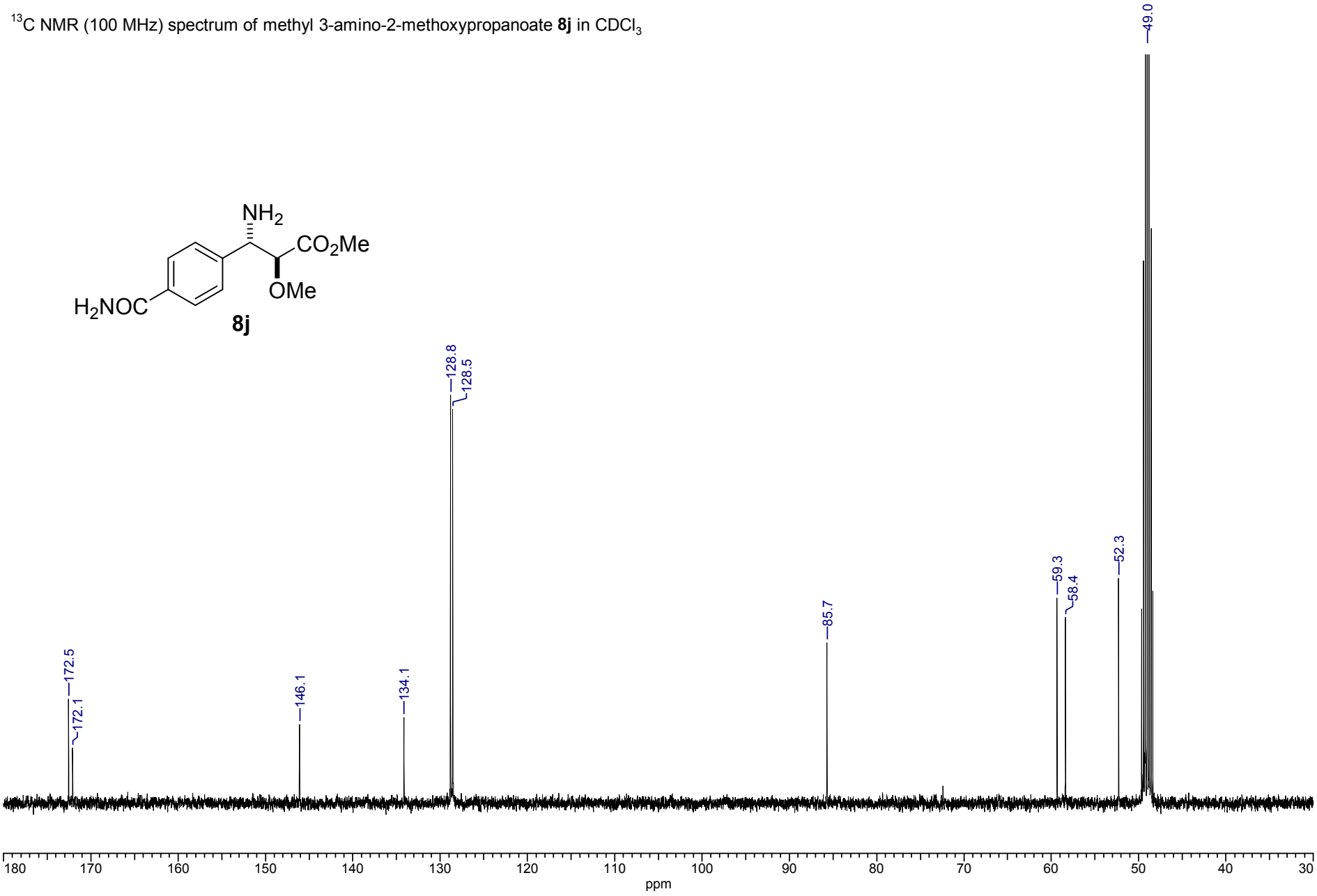
8i

^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8j** in $CDCl_3$

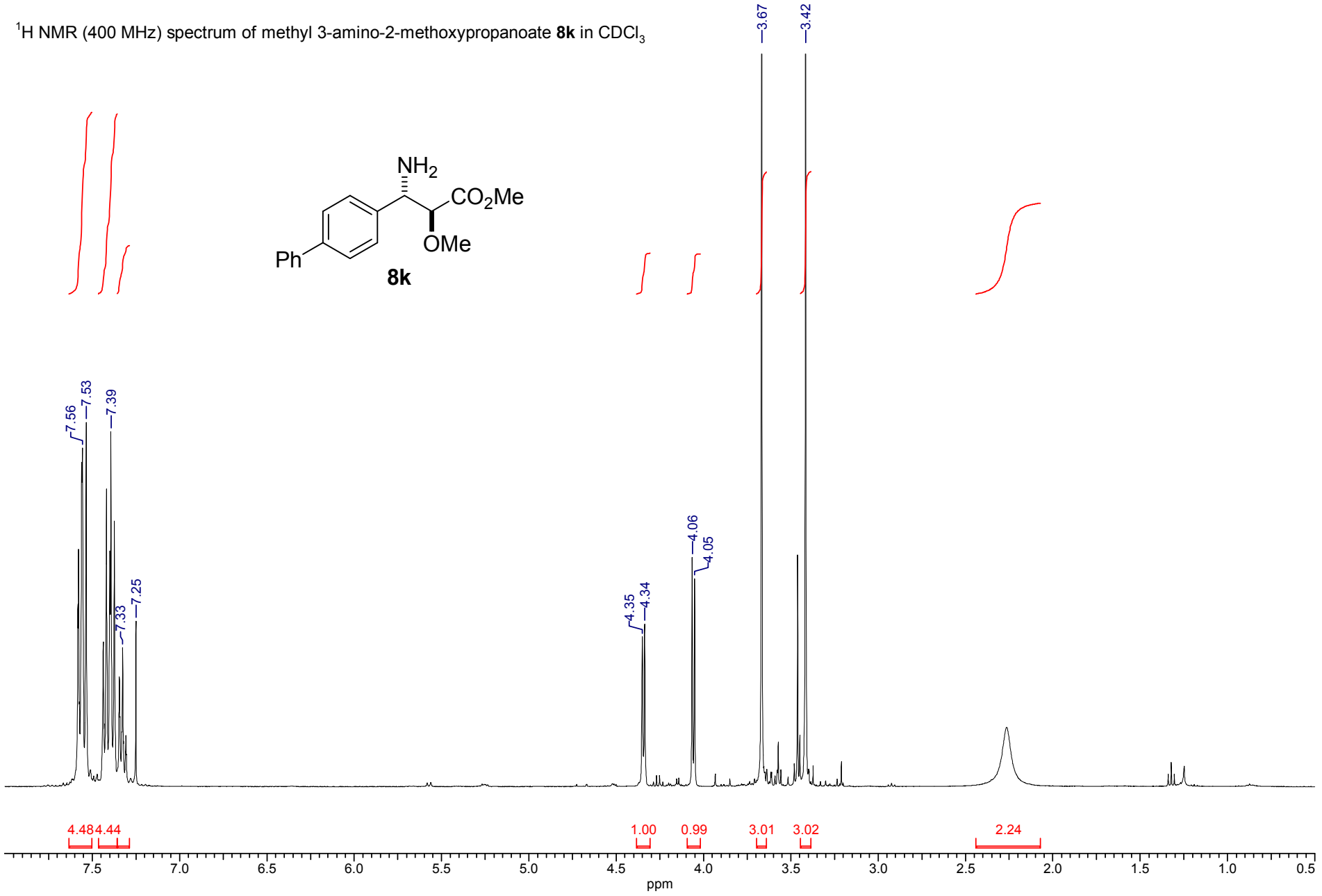


8j

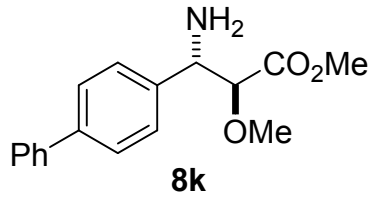
^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8j** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8k** in $CDCl_3$

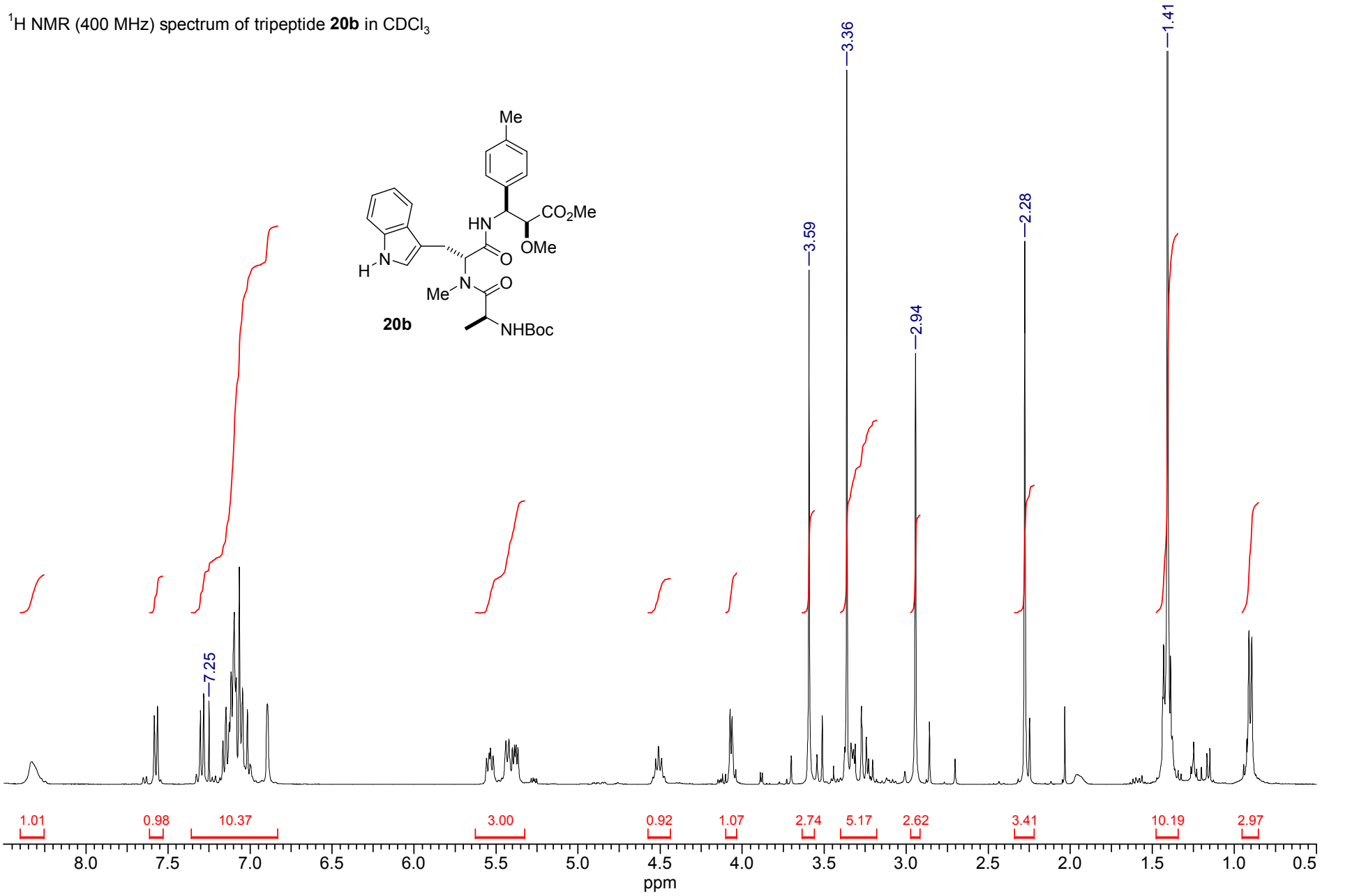


^{13}C NMR (100 MHz) spectrum of methyl 3-amino-2-methoxypropanoate **8k** in $CDCl_3$

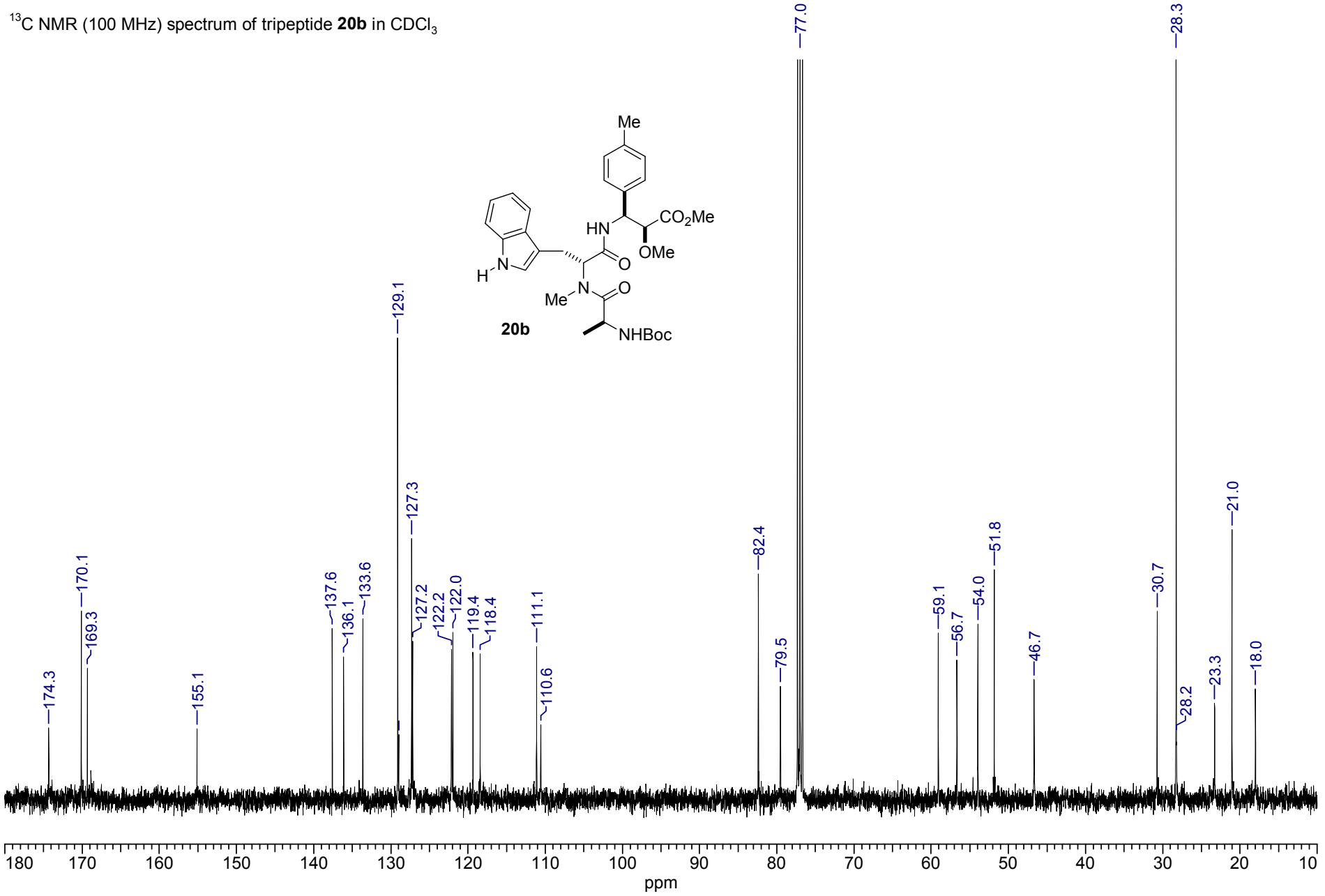


8k

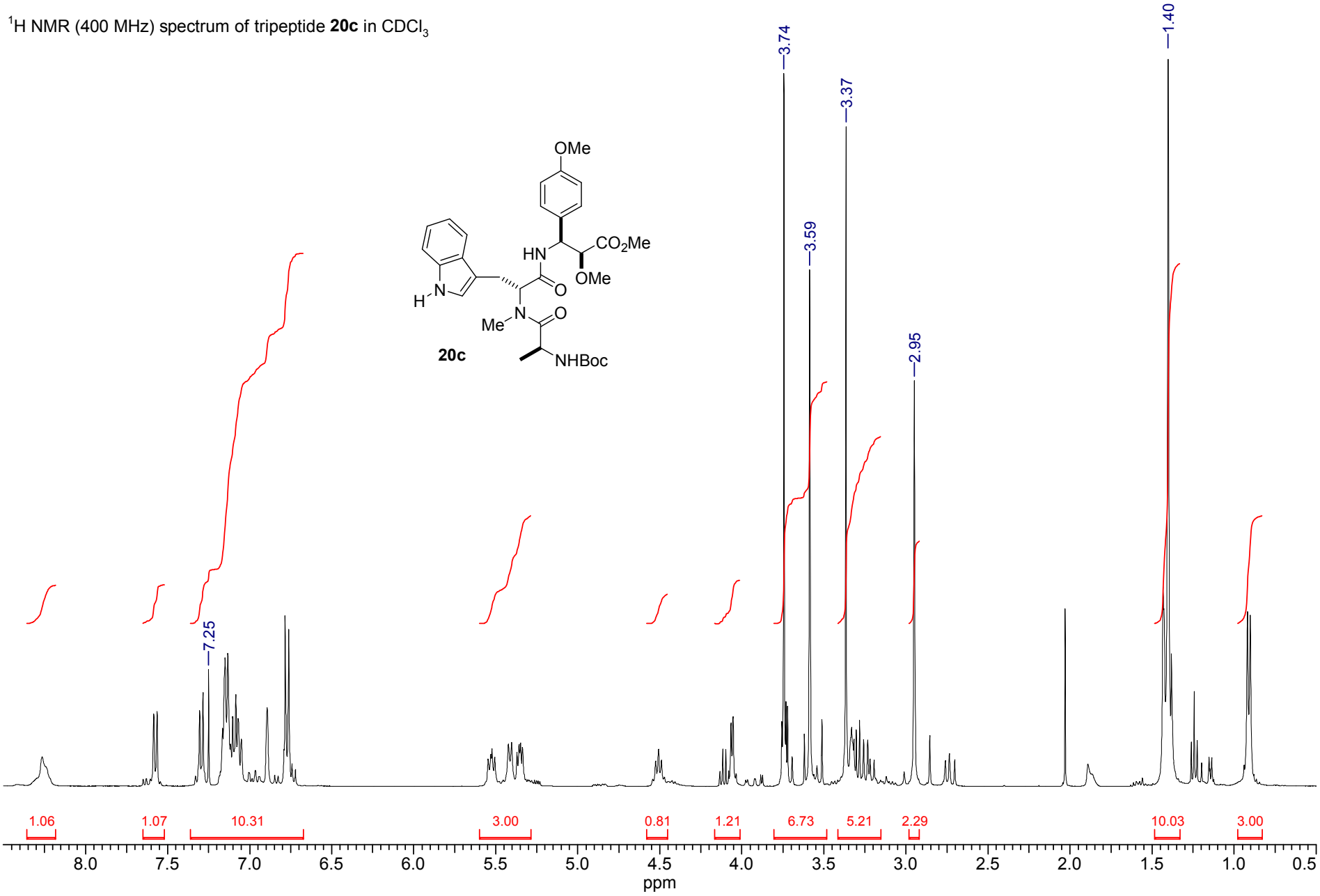
^{1}H NMR (400 MHz) spectrum of tripeptide **20b** in $CDCl_3$



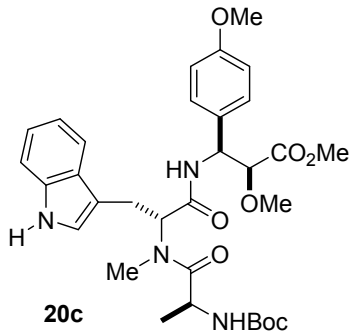
^{13}C NMR (100 MHz) spectrum of tripeptide **20b** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of tripeptide **20c** in $CDCl_3$

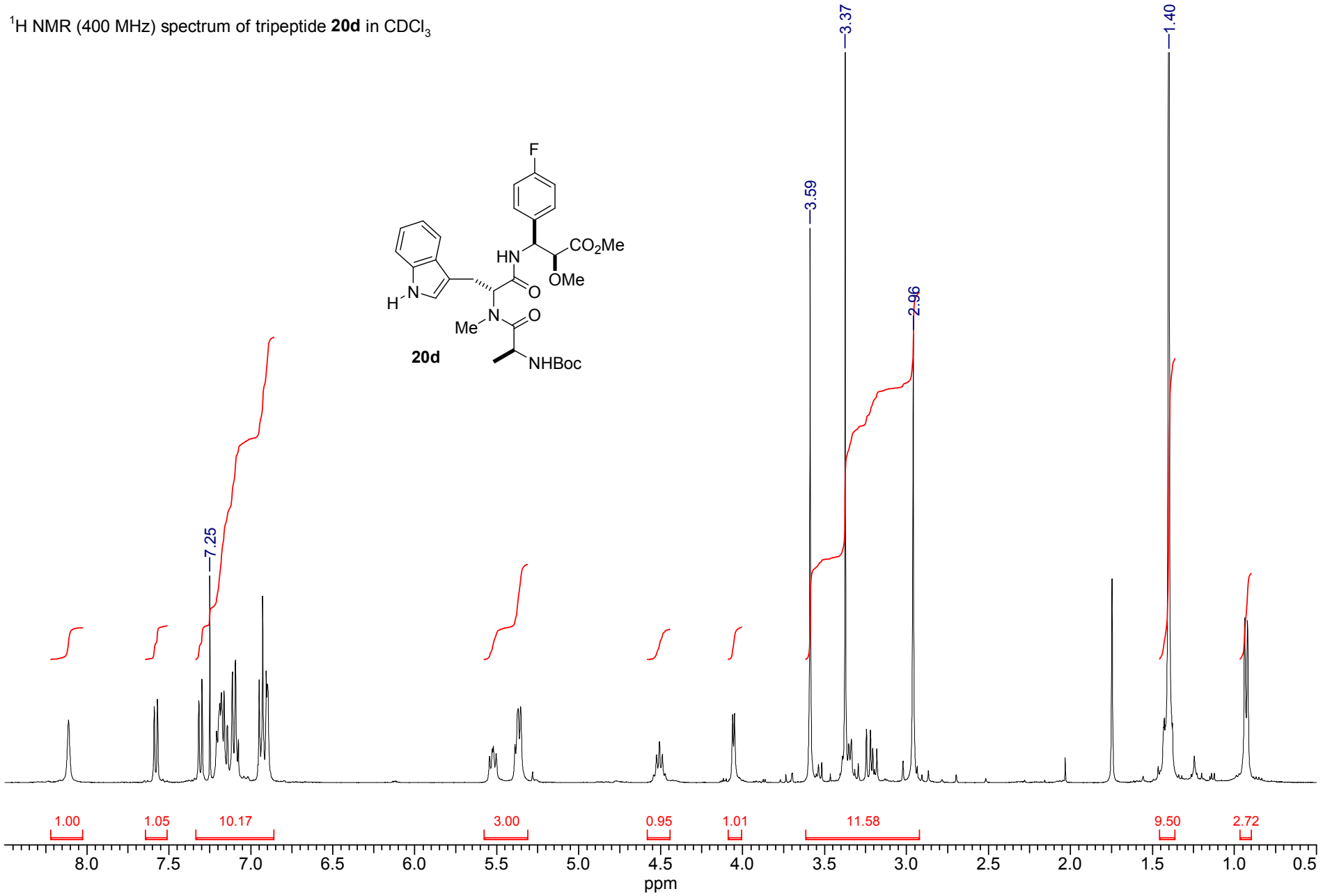


^{13}C NMR (100 MHz) spectrum of tripeptide **20c** in $CDCl_3$

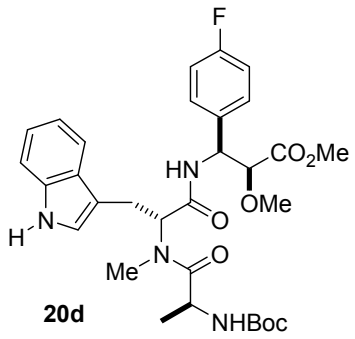


20c

^{1}H NMR (400 MHz) spectrum of tripeptide **20d** in $CDCl_3$

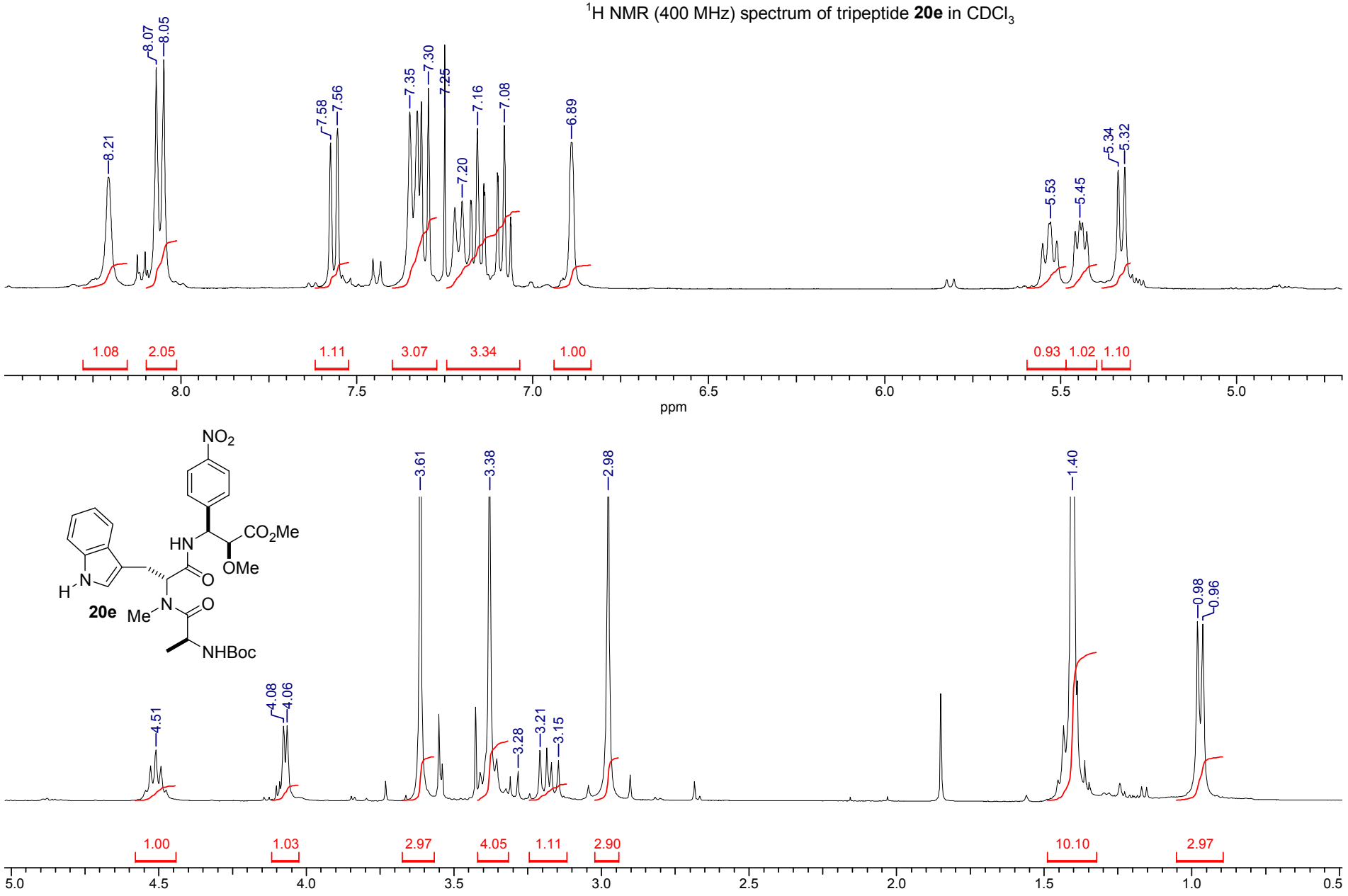


^{13}C NMR (100 MHz) spectrum of tripeptide **20d** in $CDCl_3$

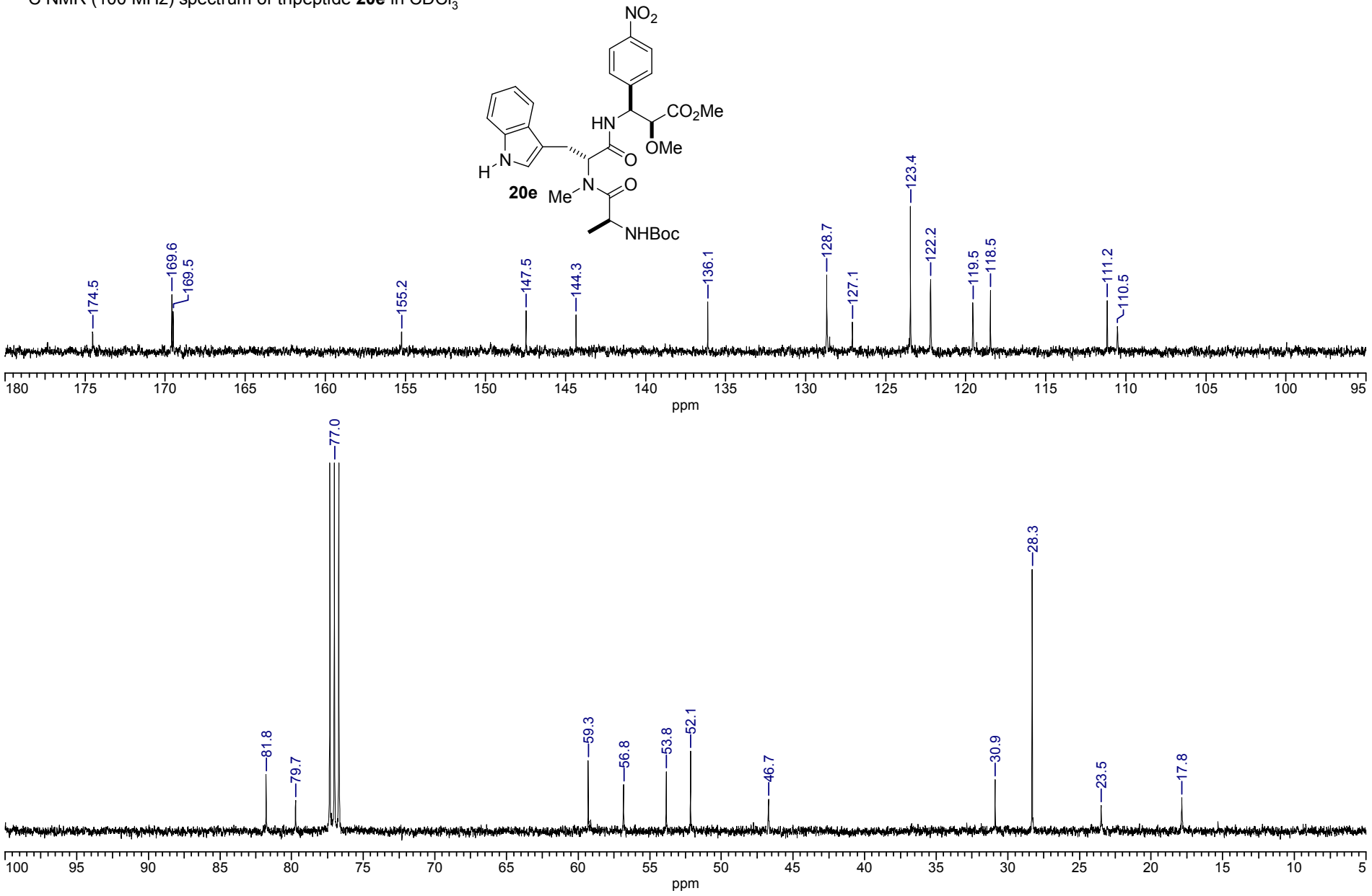


20d

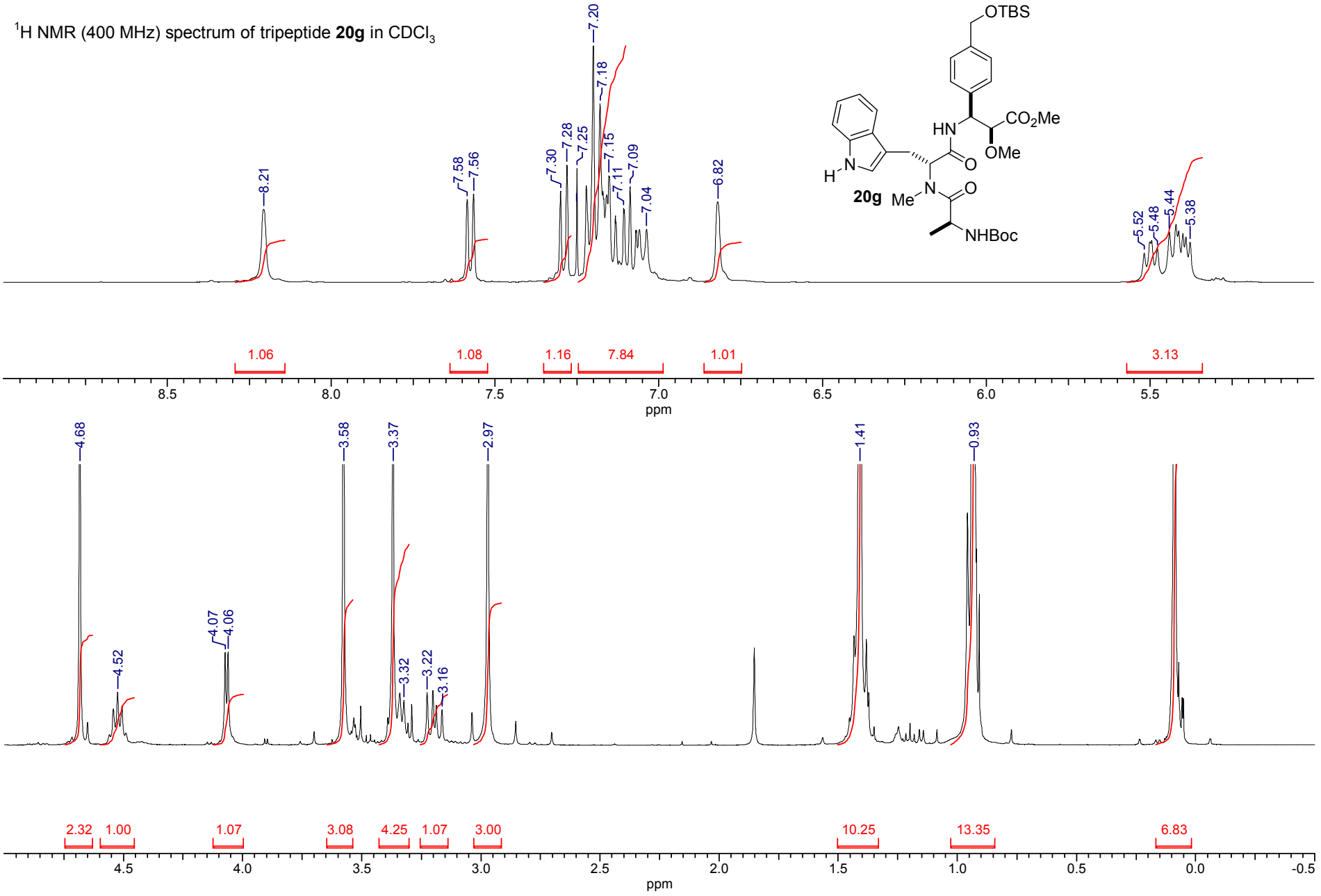
^{1}H NMR (400 MHz) spectrum of tripeptide **20e** in $CDCl_3$



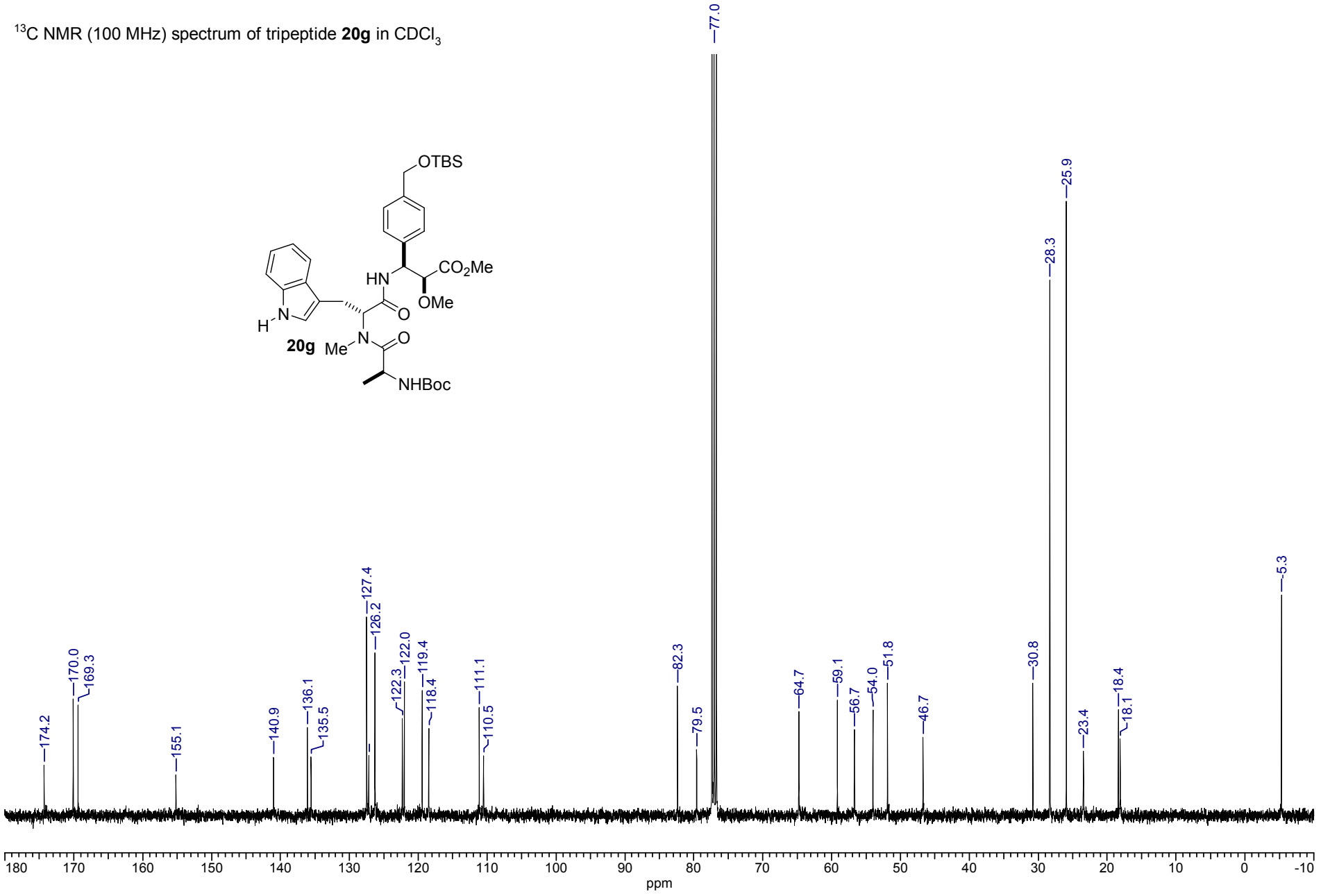
^{13}C NMR (100 MHz) spectrum of tripeptide **20e** in $CDCl_3$



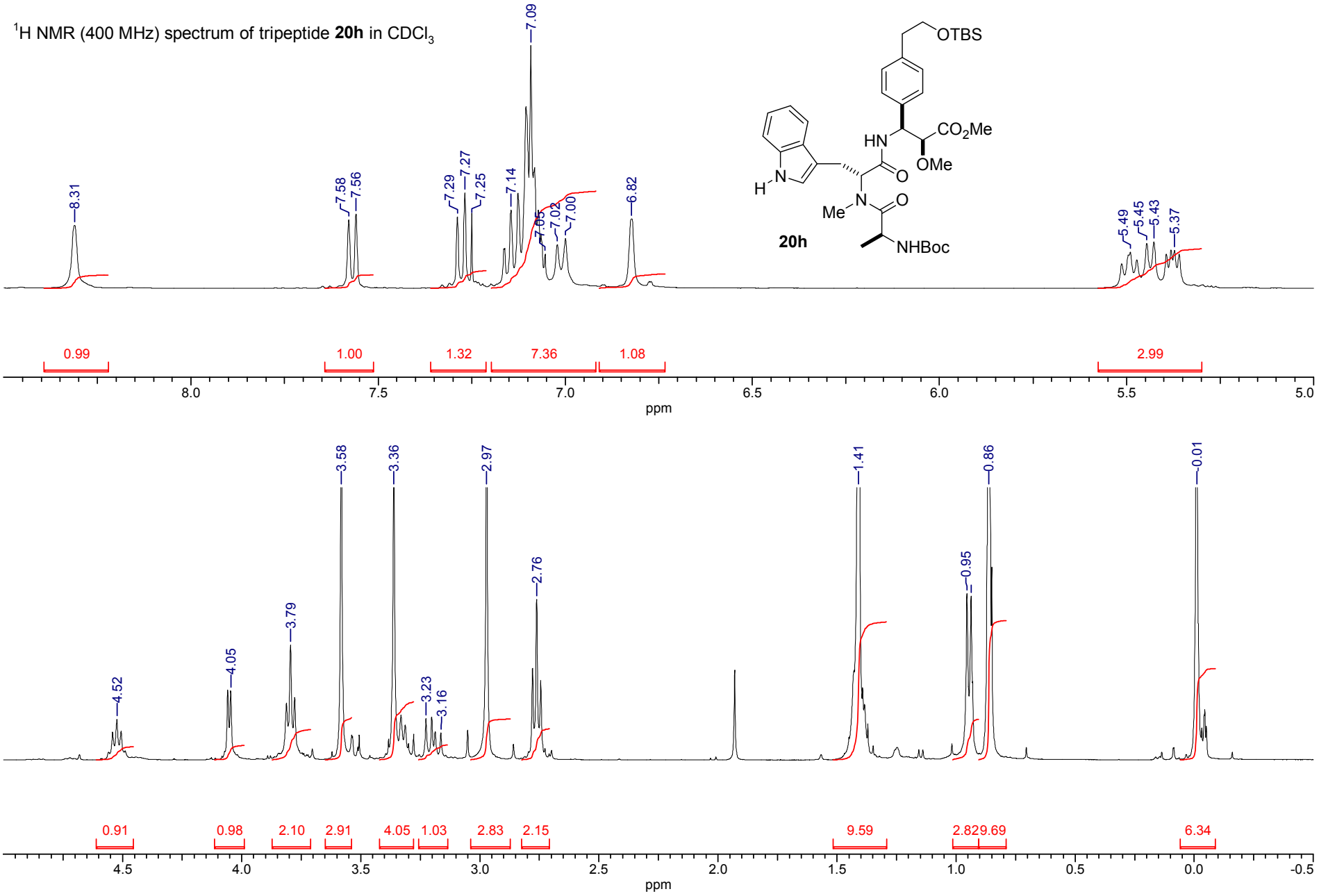
^{1}H NMR (400 MHz) spectrum of tripeptide **20g** in $CDCl_3$



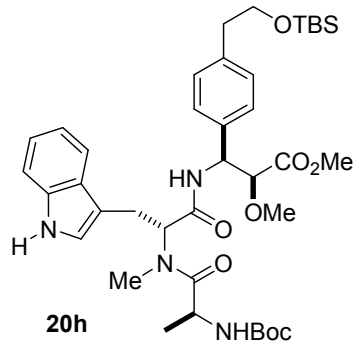
^{13}C NMR (100 MHz) spectrum of tripeptide **20g** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of tripeptide **20h** in $CDCl_3$

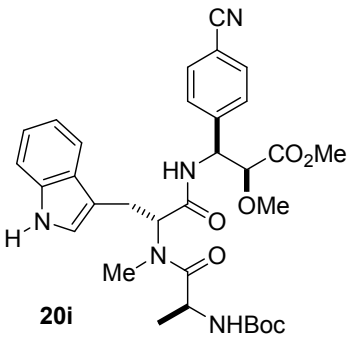


^{13}C NMR (100 MHz) spectrum of tripeptide **20h** in $CDCl_3$



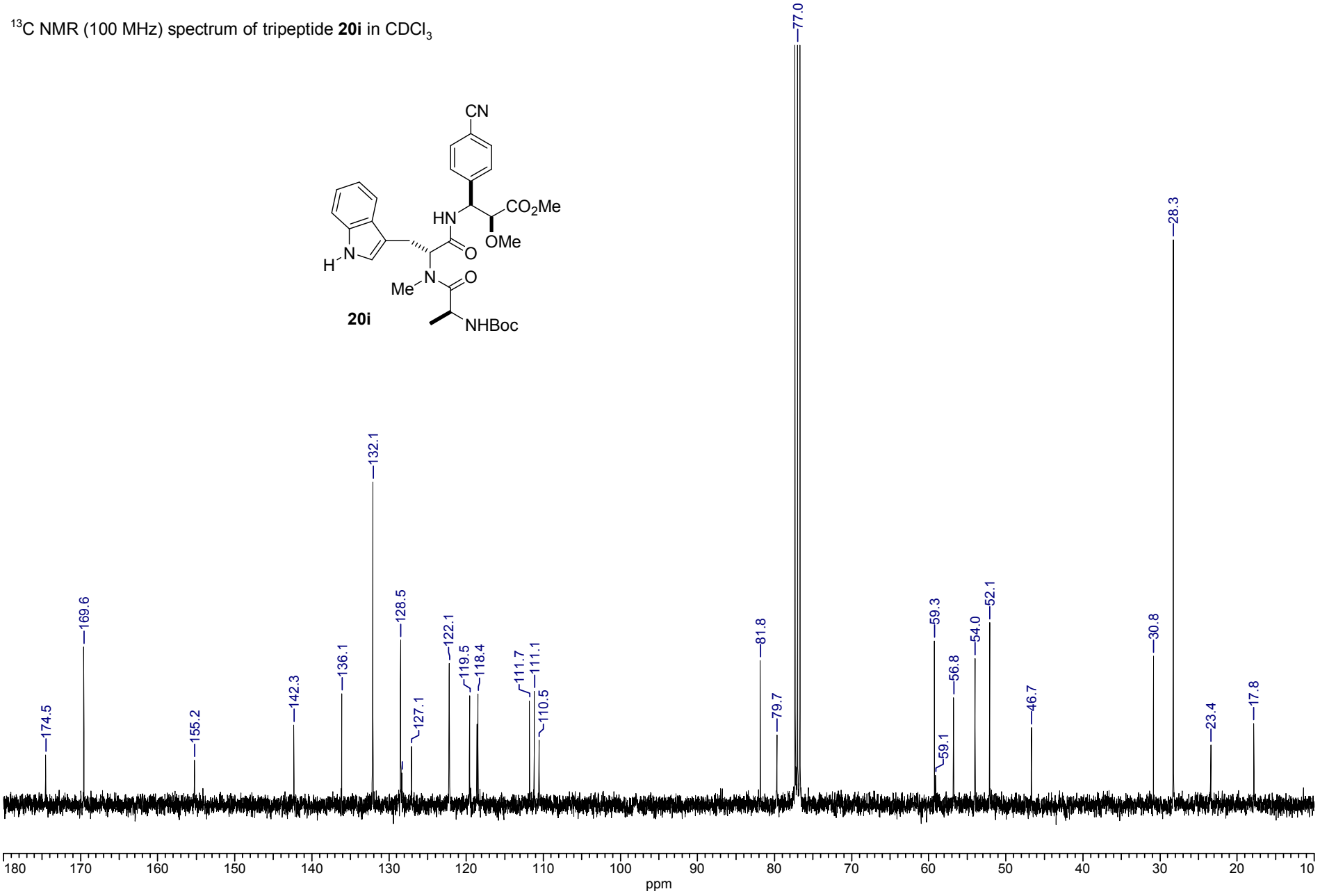
20h

^{1}H NMR (400 MHz) spectrum of tripeptide **20i** in $CDCl_3$

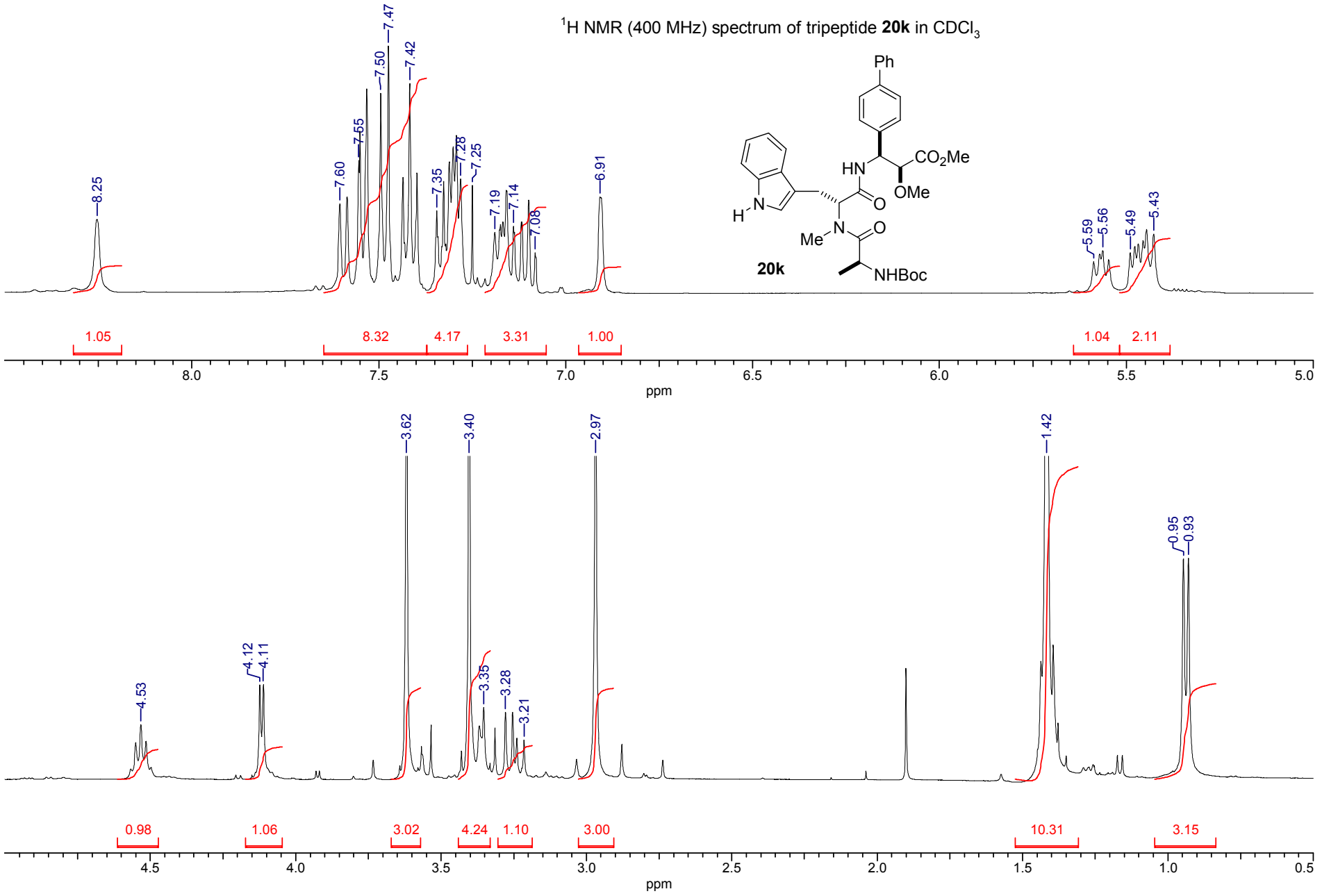


20i

^{13}C NMR (100 MHz) spectrum of tripeptide **20i** in $CDCl_3$

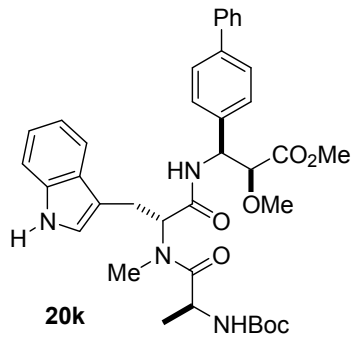


^{1}H NMR (400 MHz) spectrum of tripeptide **20k** in $CDCl_3$



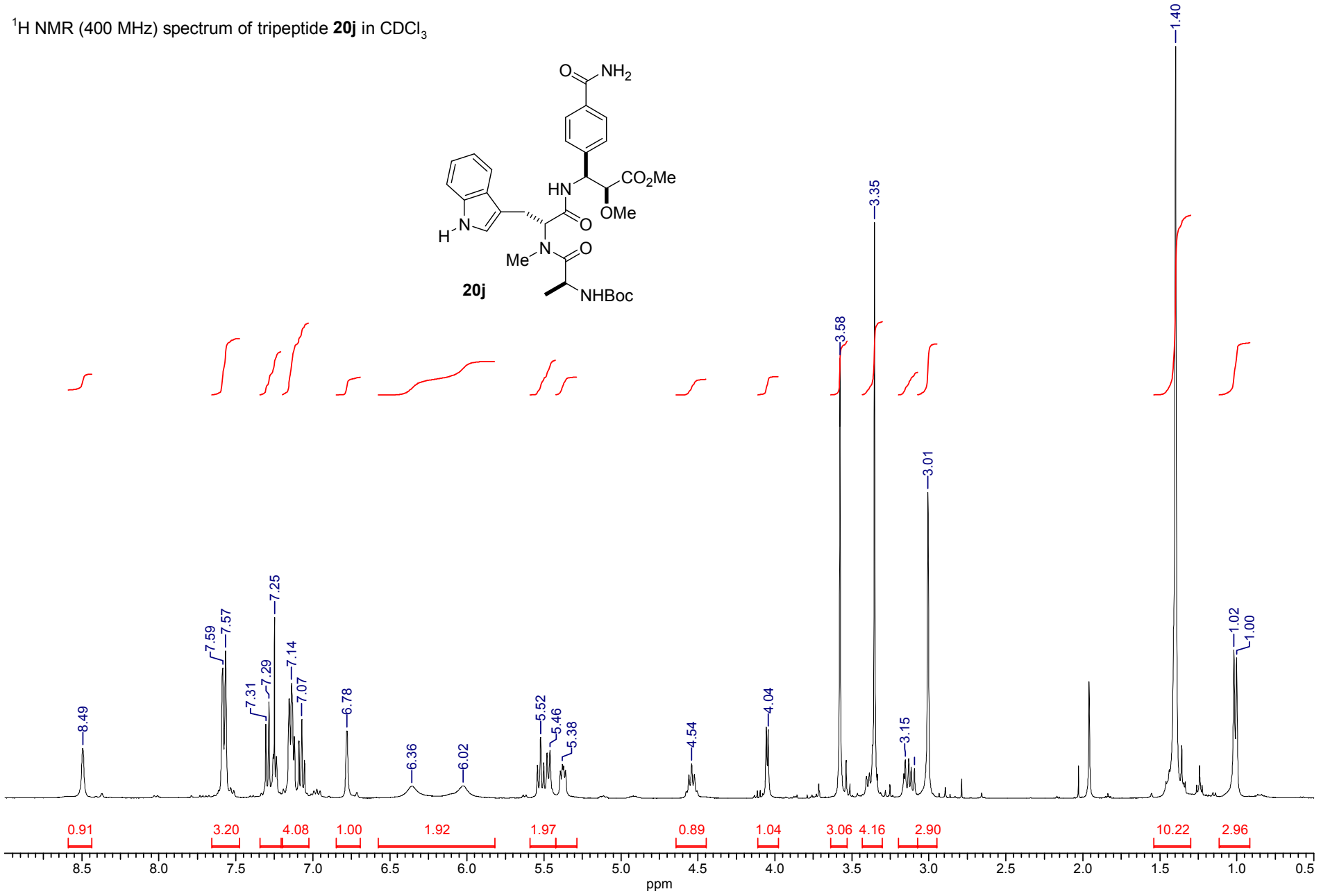
20k

^{13}C NMR (100 MHz) spectrum of tripeptide **20k** in $CDCl_3$

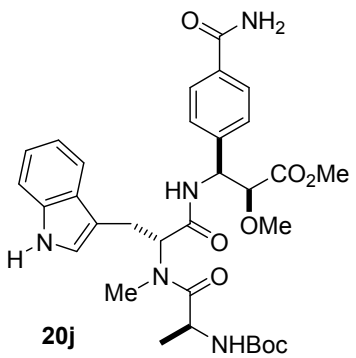


20k

^{1}H NMR (400 MHz) spectrum of tripeptide **20j** in $CDCl_3$

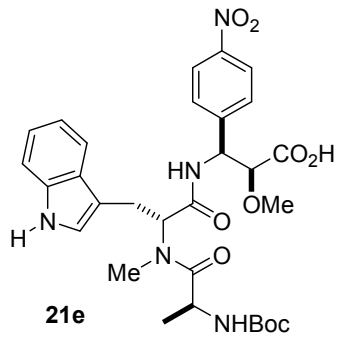


^{13}C NMR (100 MHz) spectrum of tripeptide **20j** in $CDCl_3$



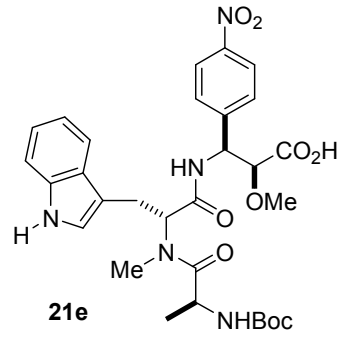
20j

^{1}H NMR (400 MHz) spectrum of tripeptide acid **21e** in $CDCl_3$



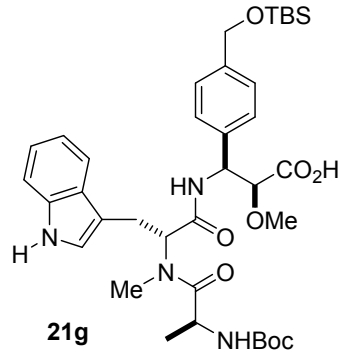
21e

^{13}C NMR (100 MHz) spectrum of tripeptide acid **21e** in $CDCl_3$



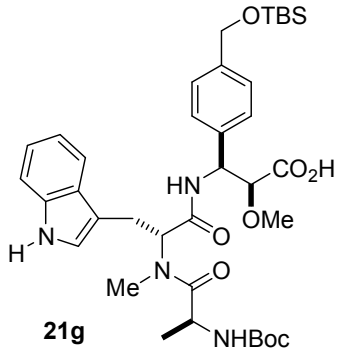
21e

^{1}H NMR (400 MHz) spectrum of tripeptide acid **21g** in $CDCl_3$



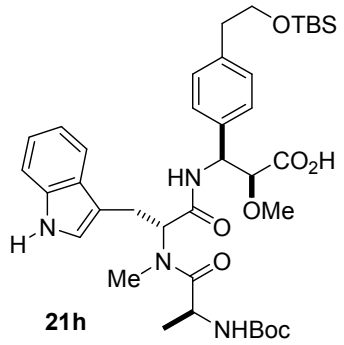
21g

^{13}C NMR (100 MHz) spectrum of tripeptide acid **21g** in $CDCl_3$



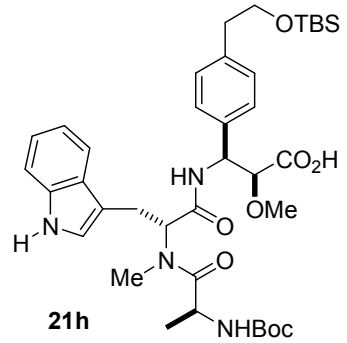
21g

^{1}H NMR (400 MHz) spectrum of tripeptide acid **21h** in $CDCl_3$



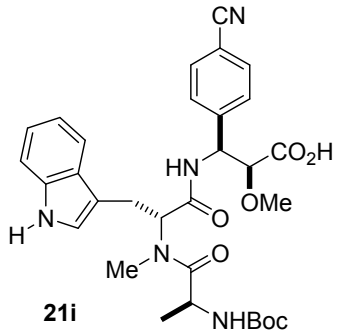
21h

^{13}C NMR (100 MHz) spectrum of tripeptide acid **21h** in $CDCl_3$



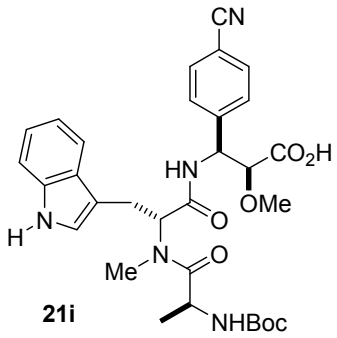
21h

^{1}H NMR (400 MHz) spectrum of tripeptide acid **21i** in $CDCl_3$



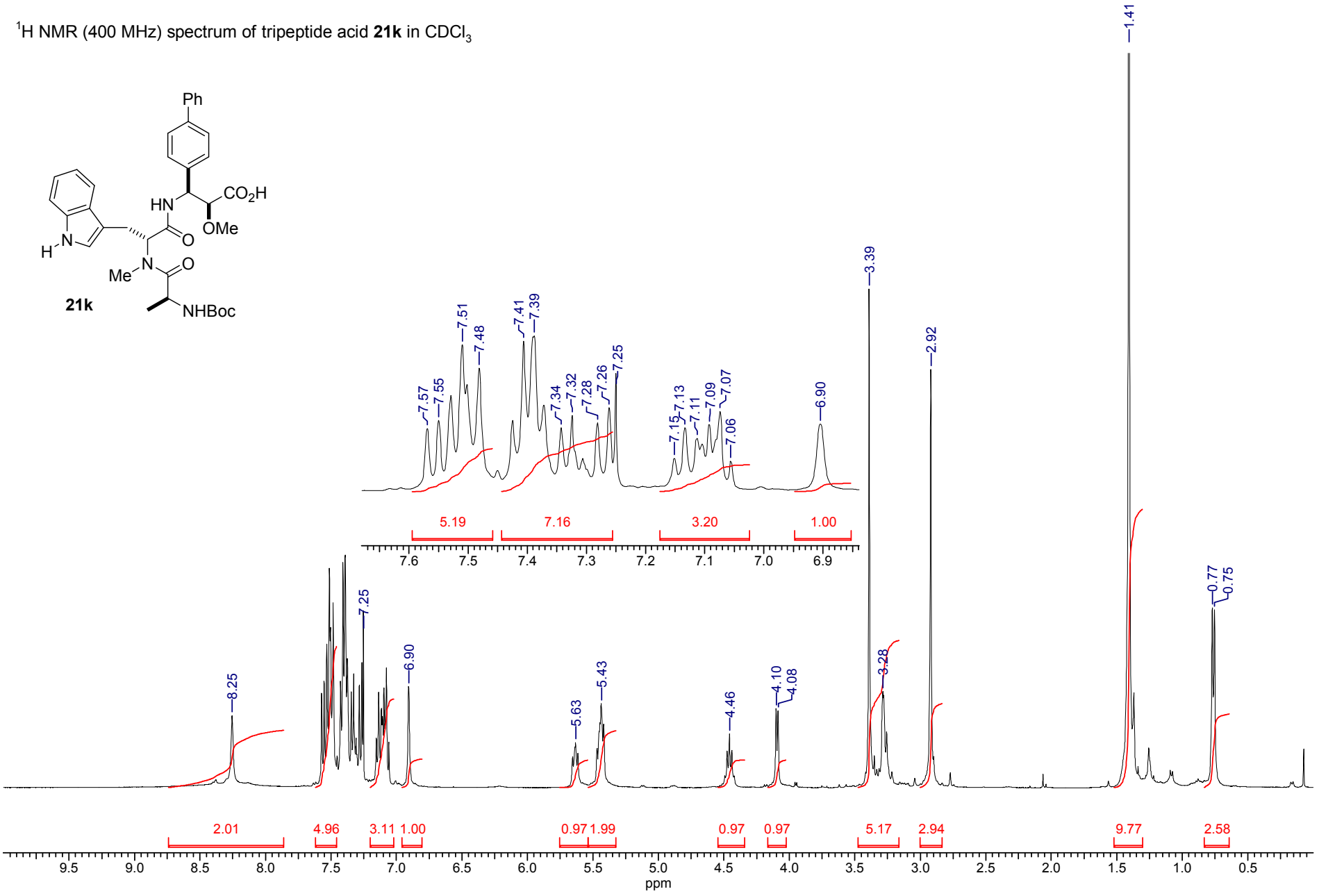
21i

^{13}C NMR (100 MHz) spectrum of tripeptide acid **21i** in $CDCl_3$

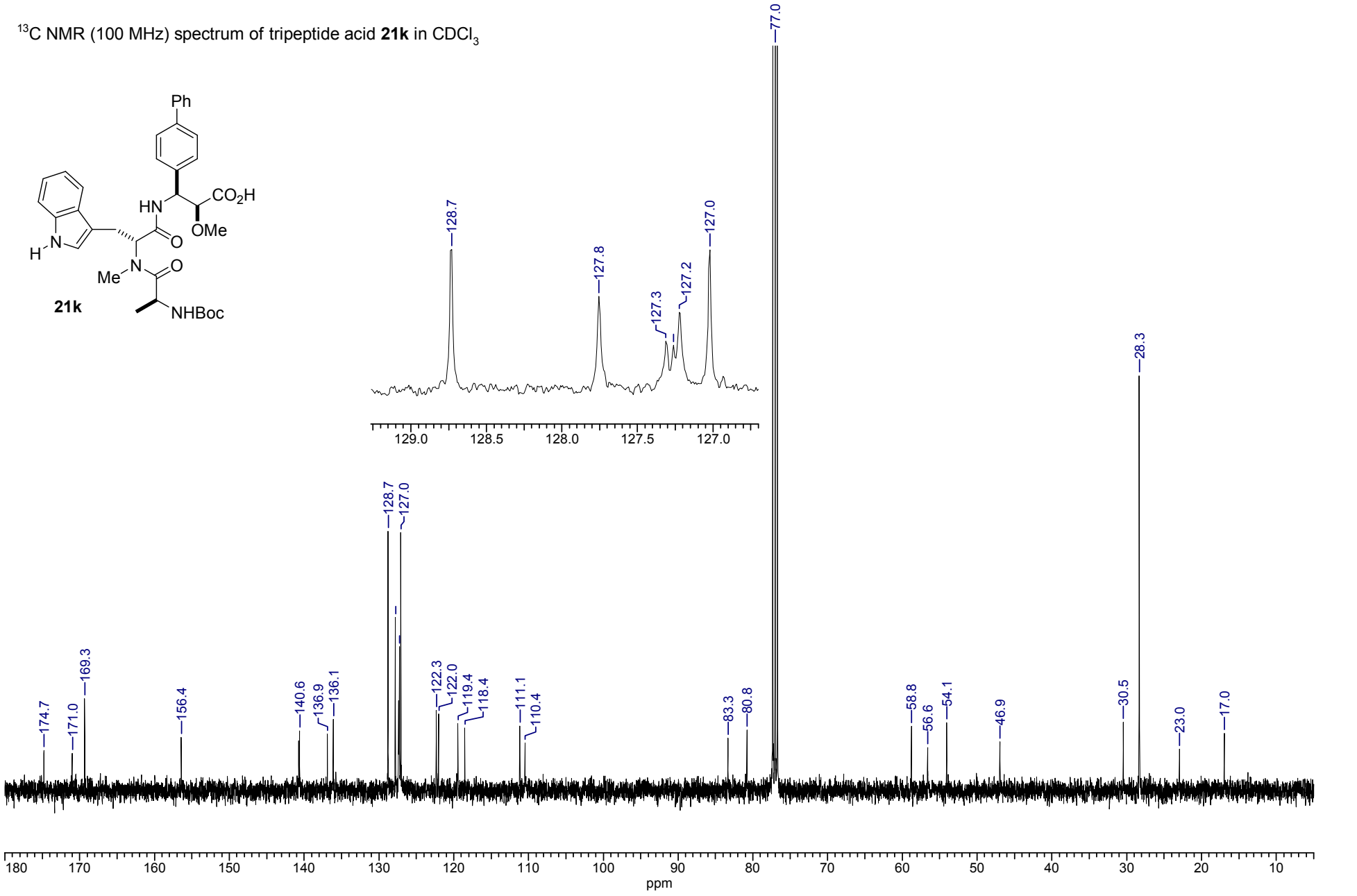


21i

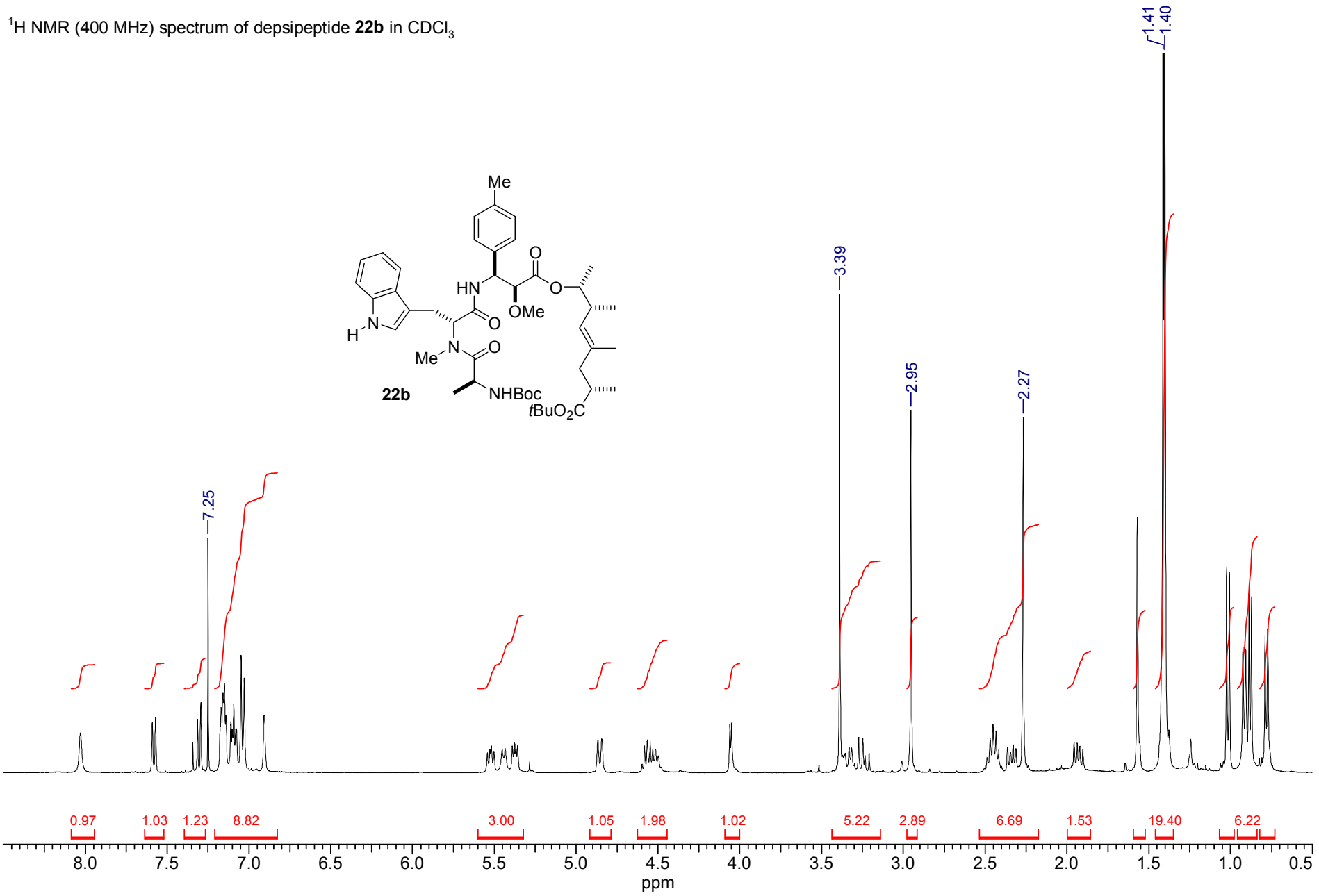
^{1}H NMR (400 MHz) spectrum of tripeptide acid **21k** in $CDCl_3$



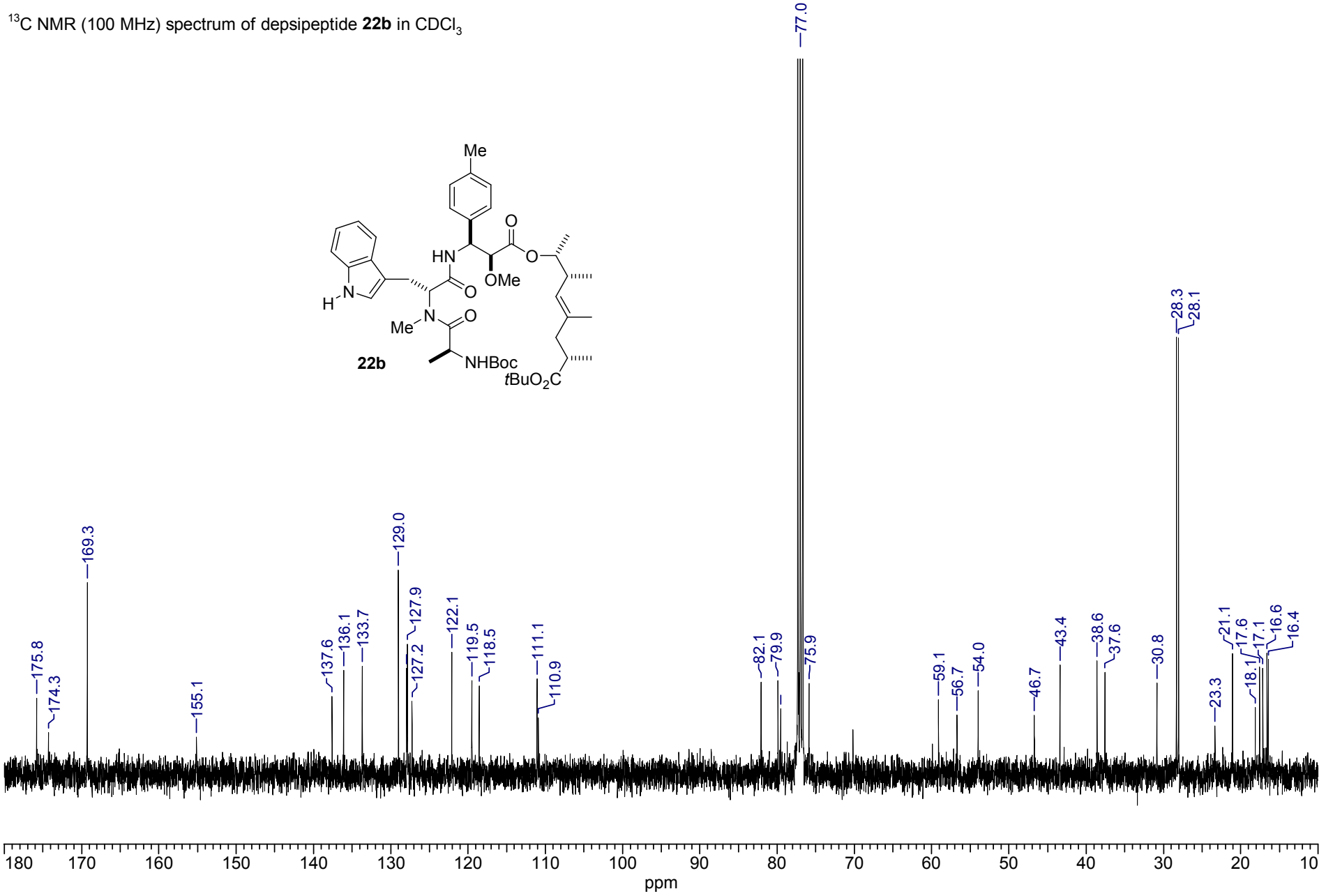
^{13}C NMR (100 MHz) spectrum of tripeptide acid **21k** in $CDCl_3$



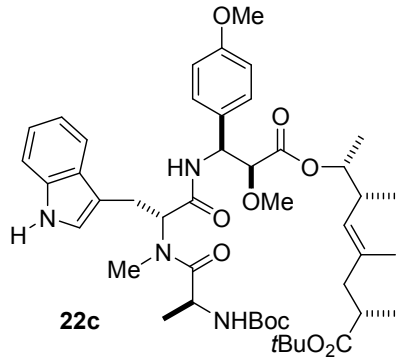
^{1}H NMR (400 MHz) spectrum of depsipeptide **22b** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of depsipeptide **22b** in $CDCl_3$

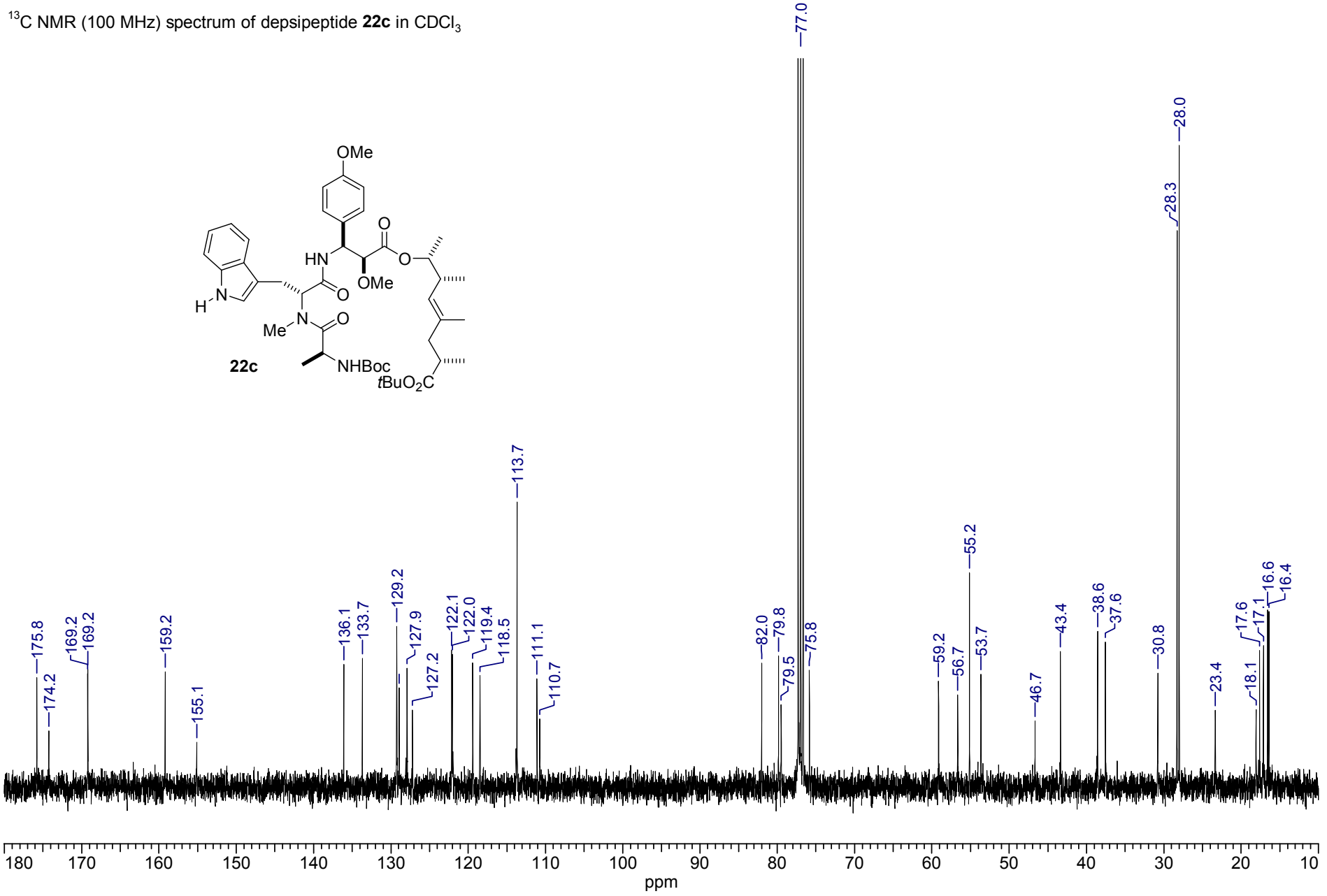


^{1}H NMR (400 MHz) spectrum of depsipeptide **22c** in $CDCl_3$

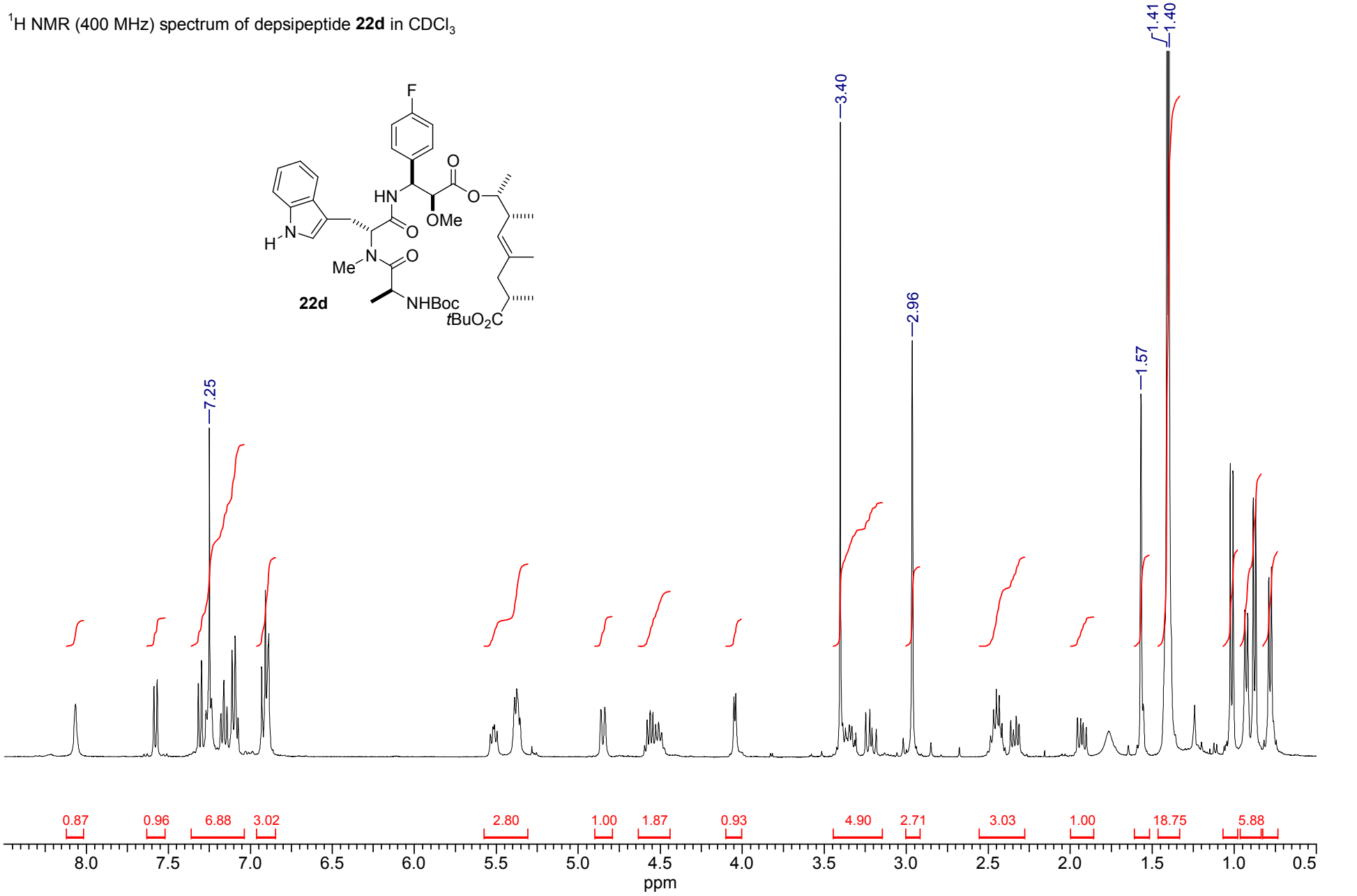


22c

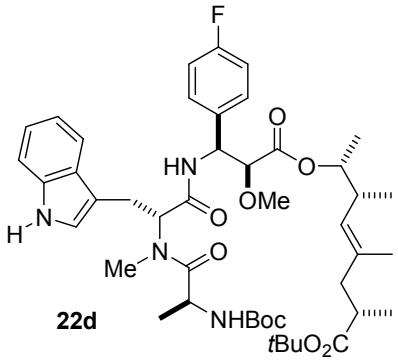
^{13}C NMR (100 MHz) spectrum of depsipeptide **22c** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of depsipeptide **22d** in $CDCl_3$

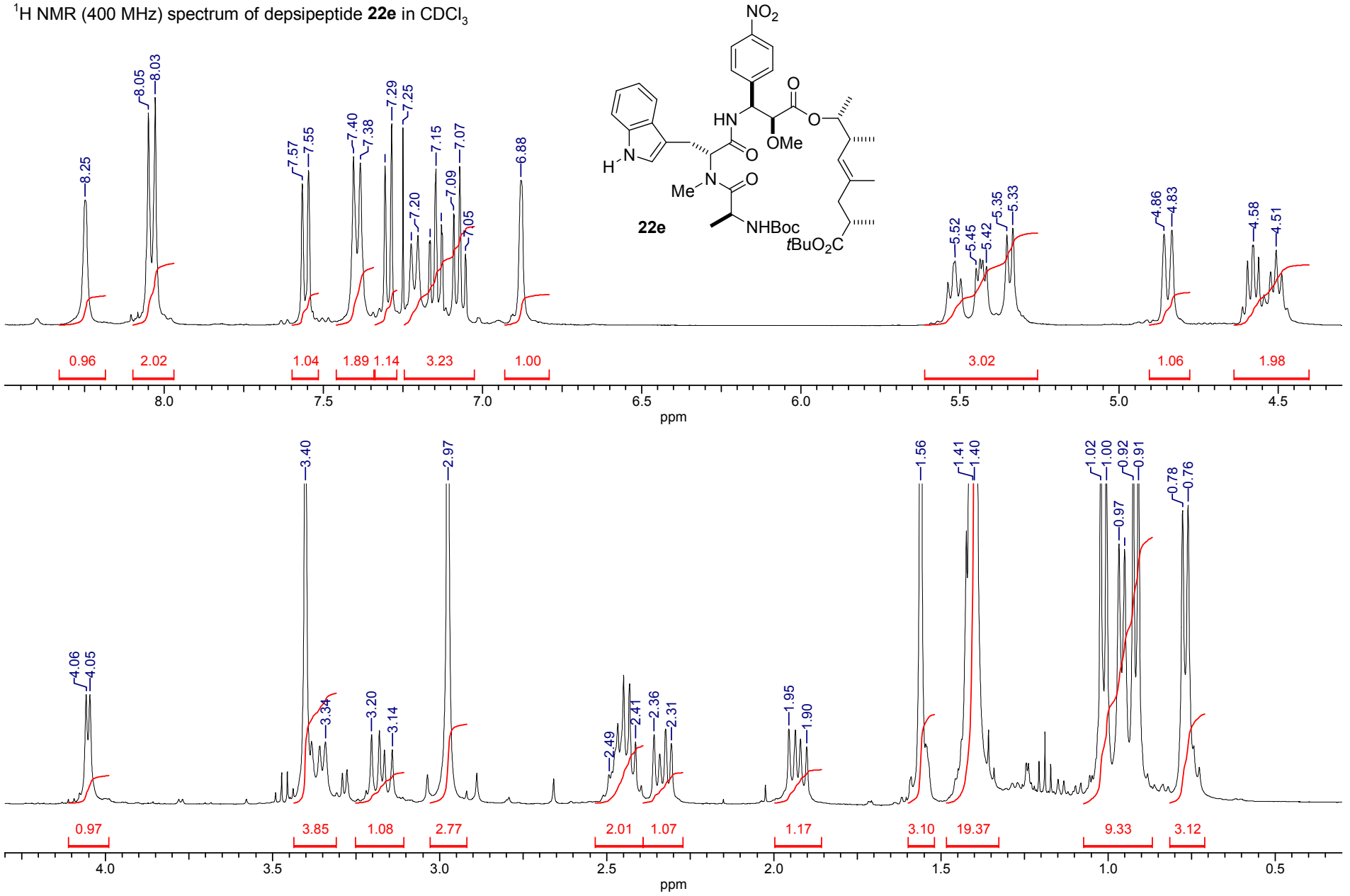


^{13}C NMR (100 MHz) spectrum of depsipeptide **22d** in $CDCl_3$

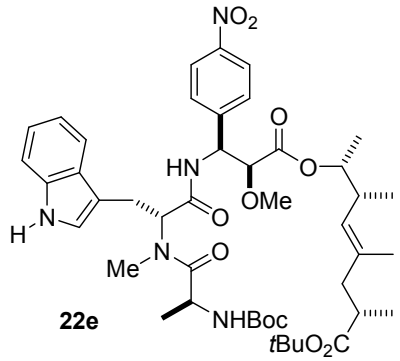


22d

^{1}H NMR (400 MHz) spectrum of depsipeptide **22e** in $CDCl_3$

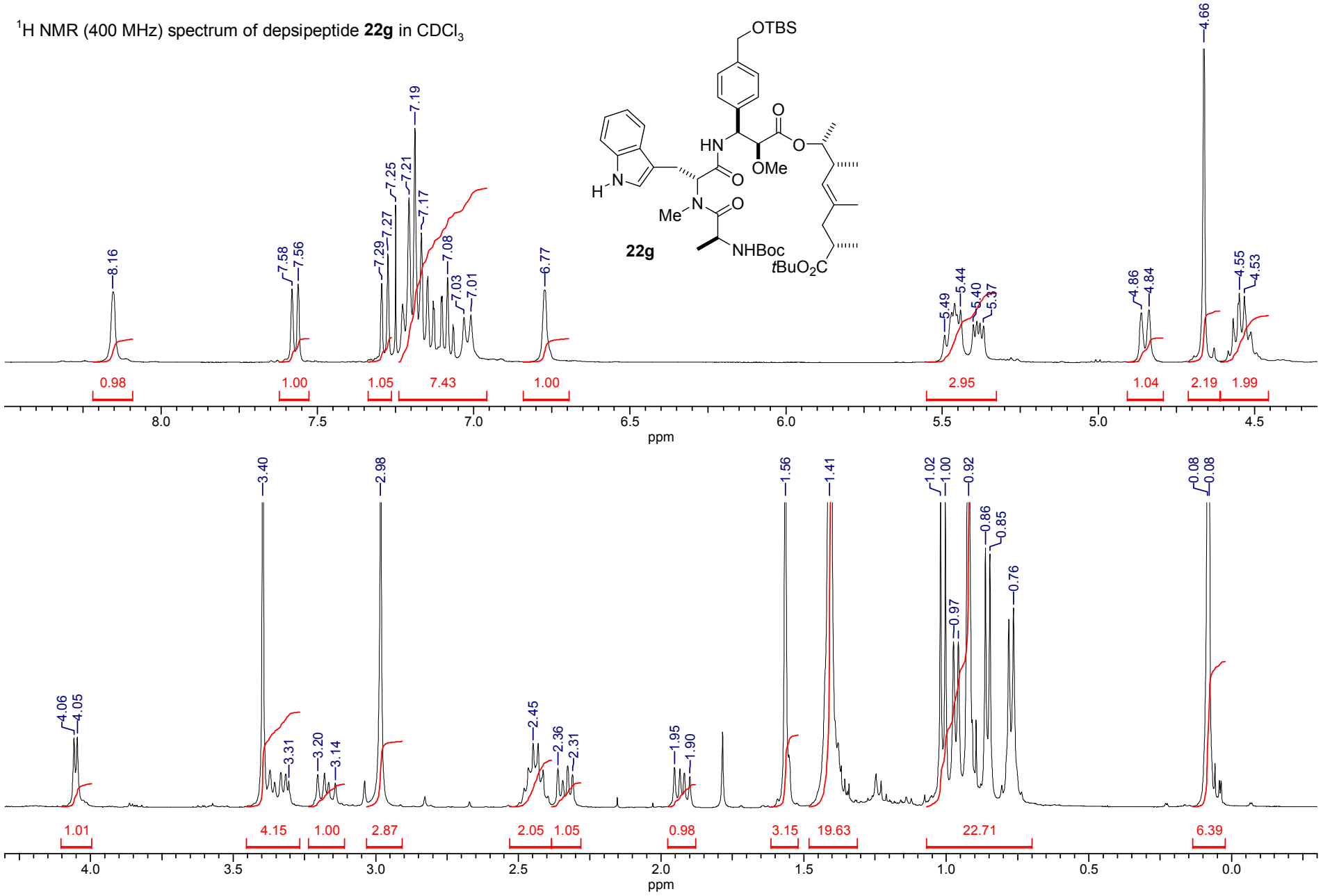


^{13}C NMR (100 MHz) spectrum of depsipeptide **22e** in $CDCl_3$

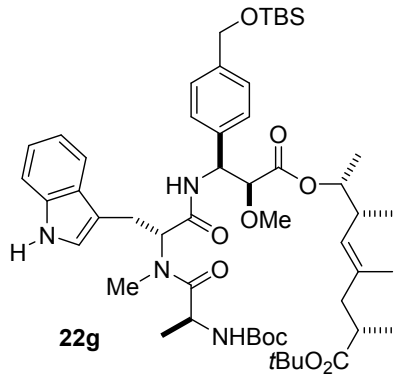


22e

^{1}H NMR (400 MHz) spectrum of depsipeptide **22g** in $CDCl_3$

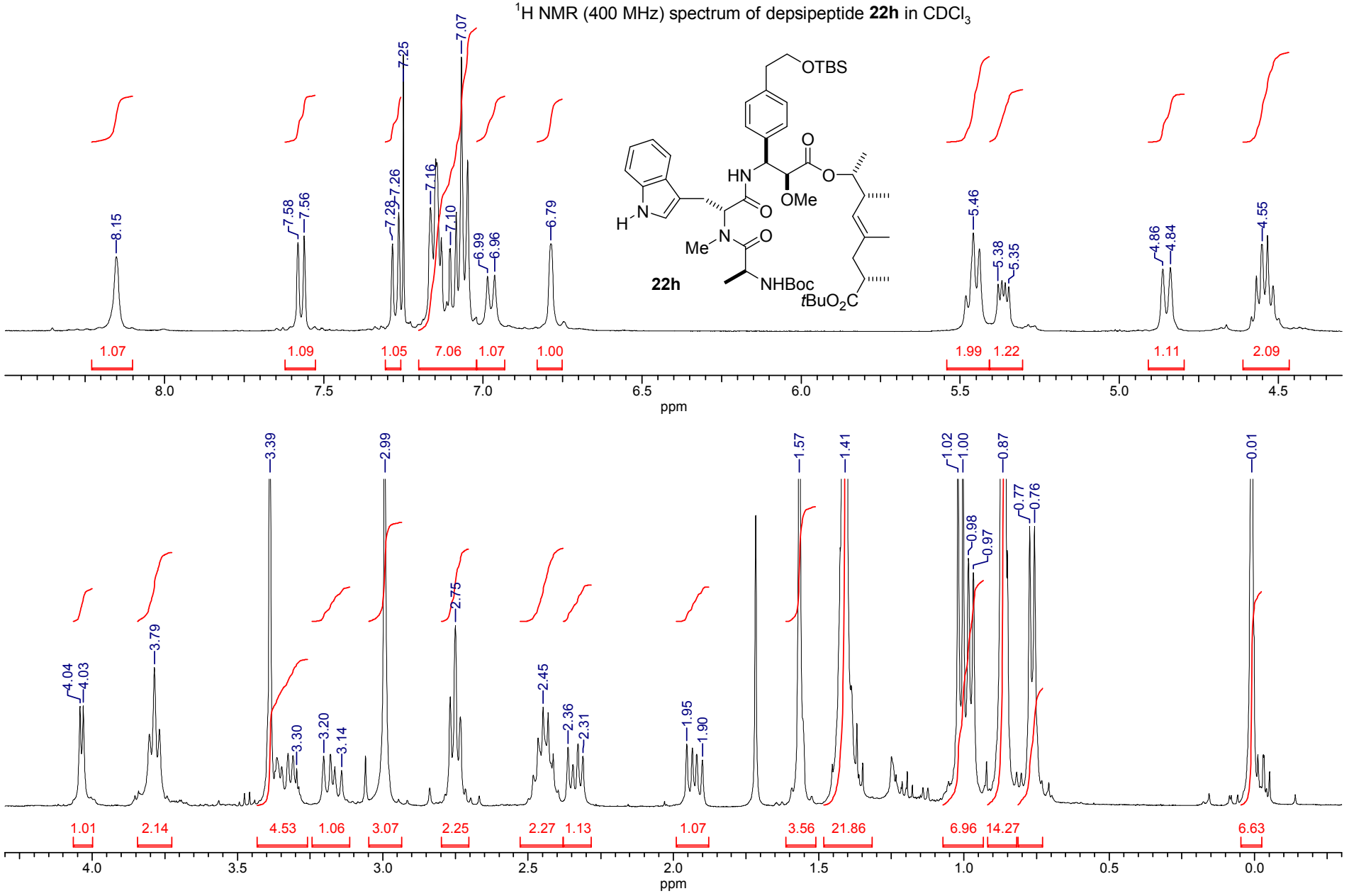


^{13}C NMR (100 MHz) spectrum of depsipeptide **22g** in $CDCl_3$

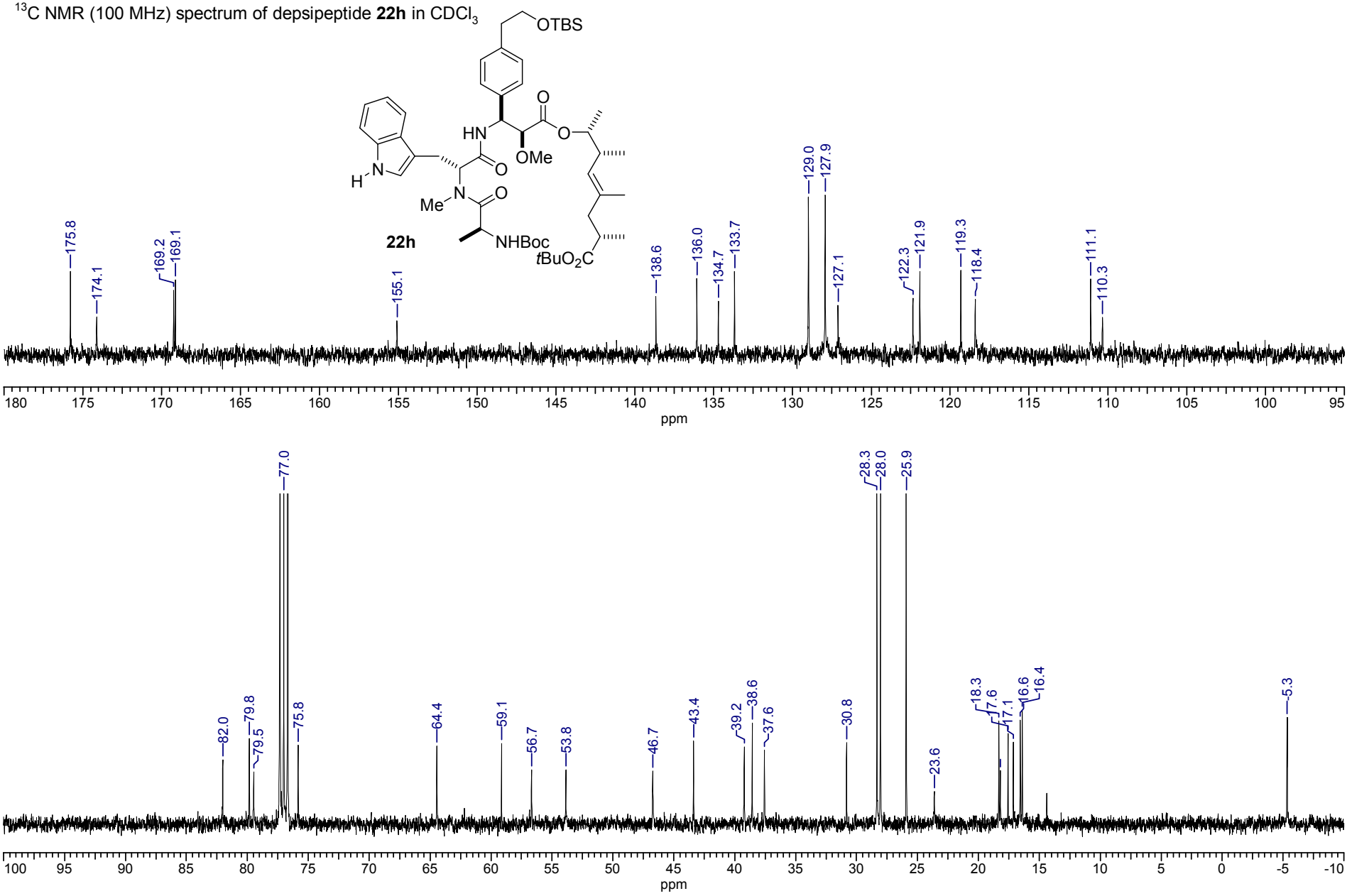


22g

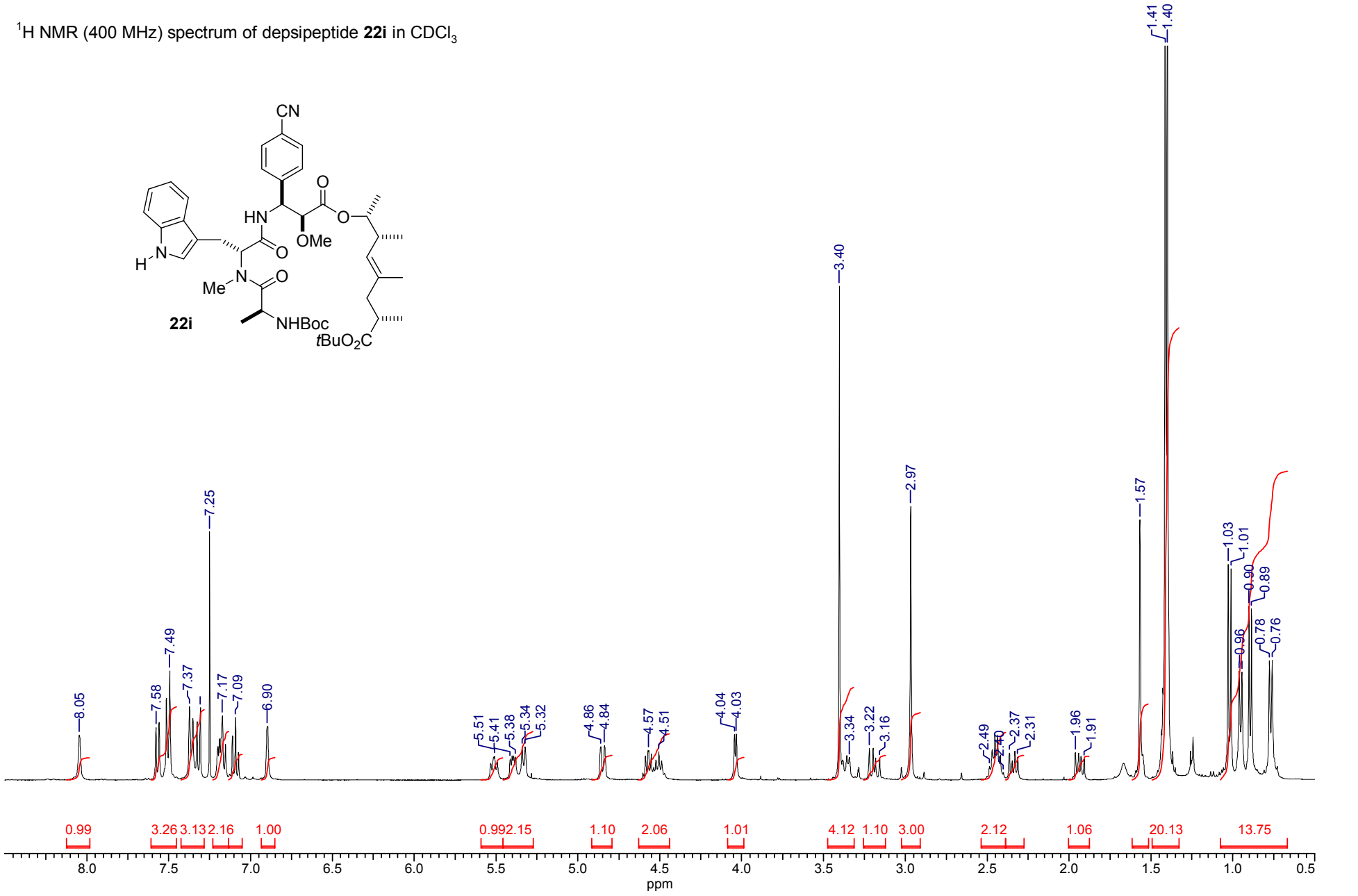
^{1}H NMR (400 MHz) spectrum of depsipeptide **22h** in $CDCl_3$



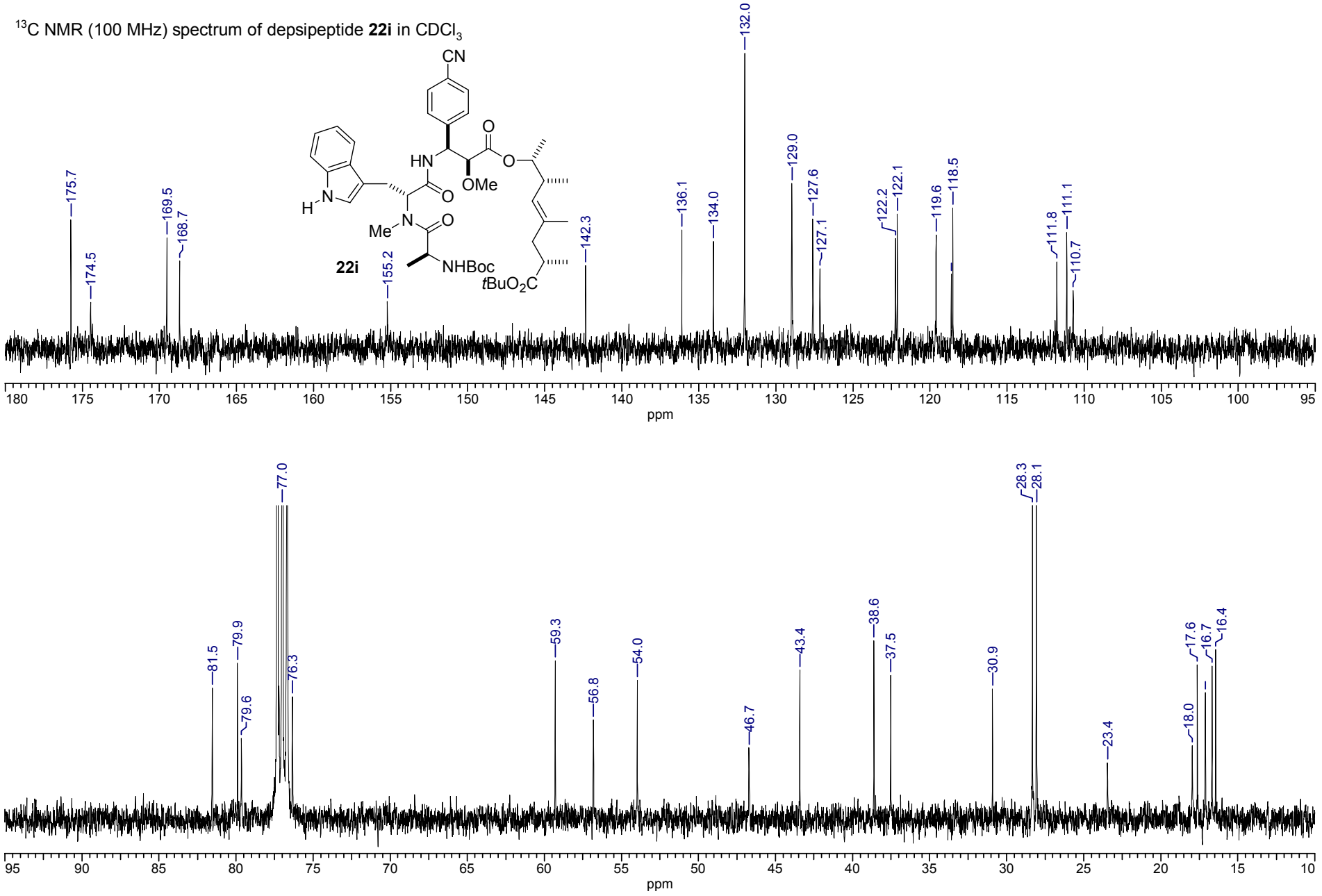
^{13}C NMR (100 MHz) spectrum of depsipeptide **22h** in $CDCl_3$



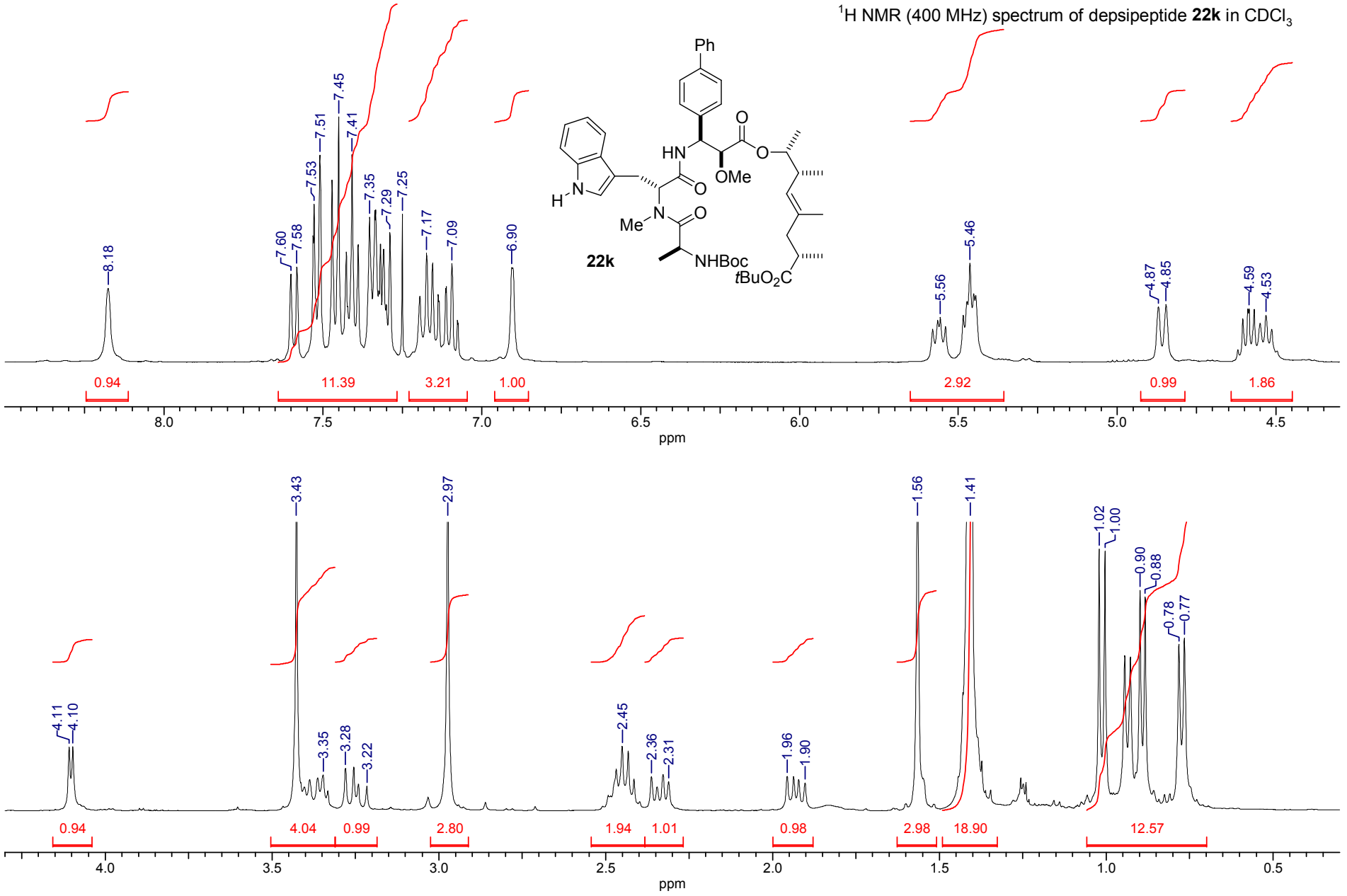
^{1}H NMR (400 MHz) spectrum of depsipeptide **22i** in $CDCl_3$



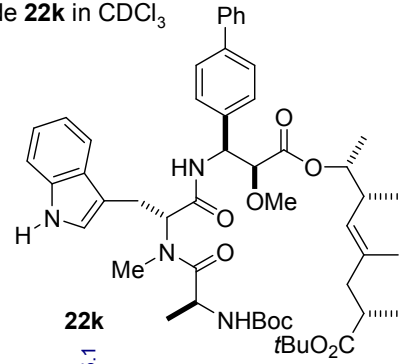
^{13}C NMR (100 MHz) spectrum of depsipeptide **22i** in $CDCl_3$



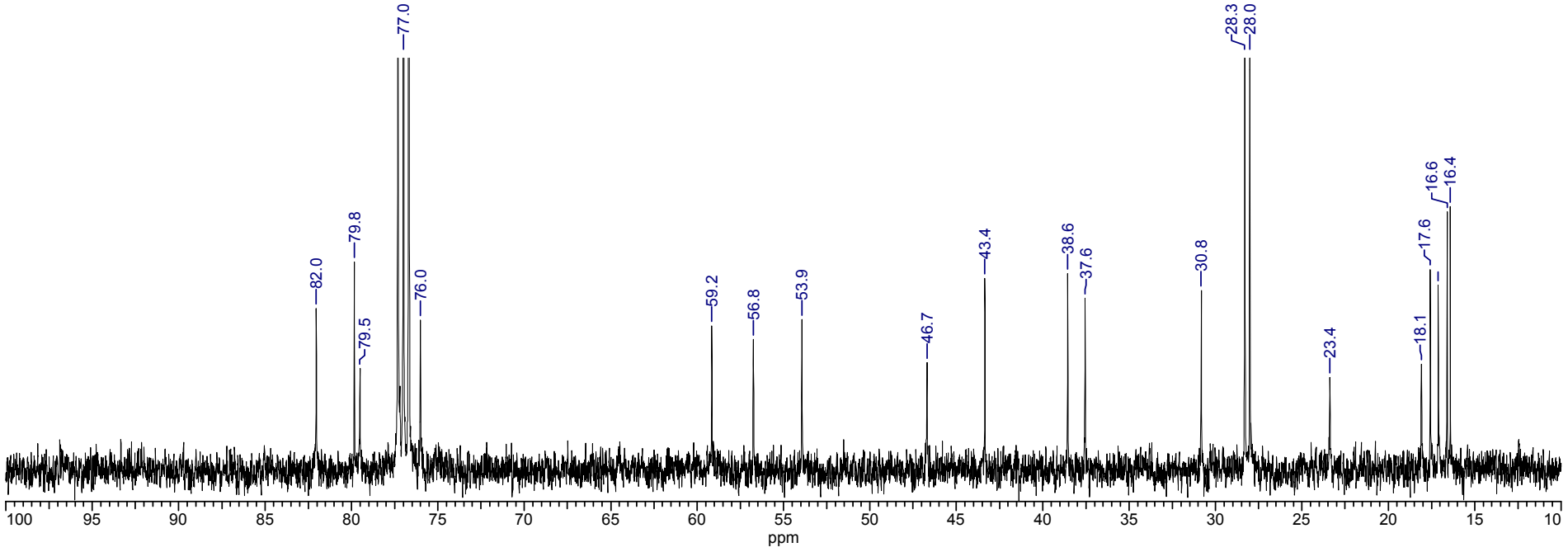
^{1}H NMR (400 MHz) spectrum of depsipeptide **22k** in $CDCl_3$



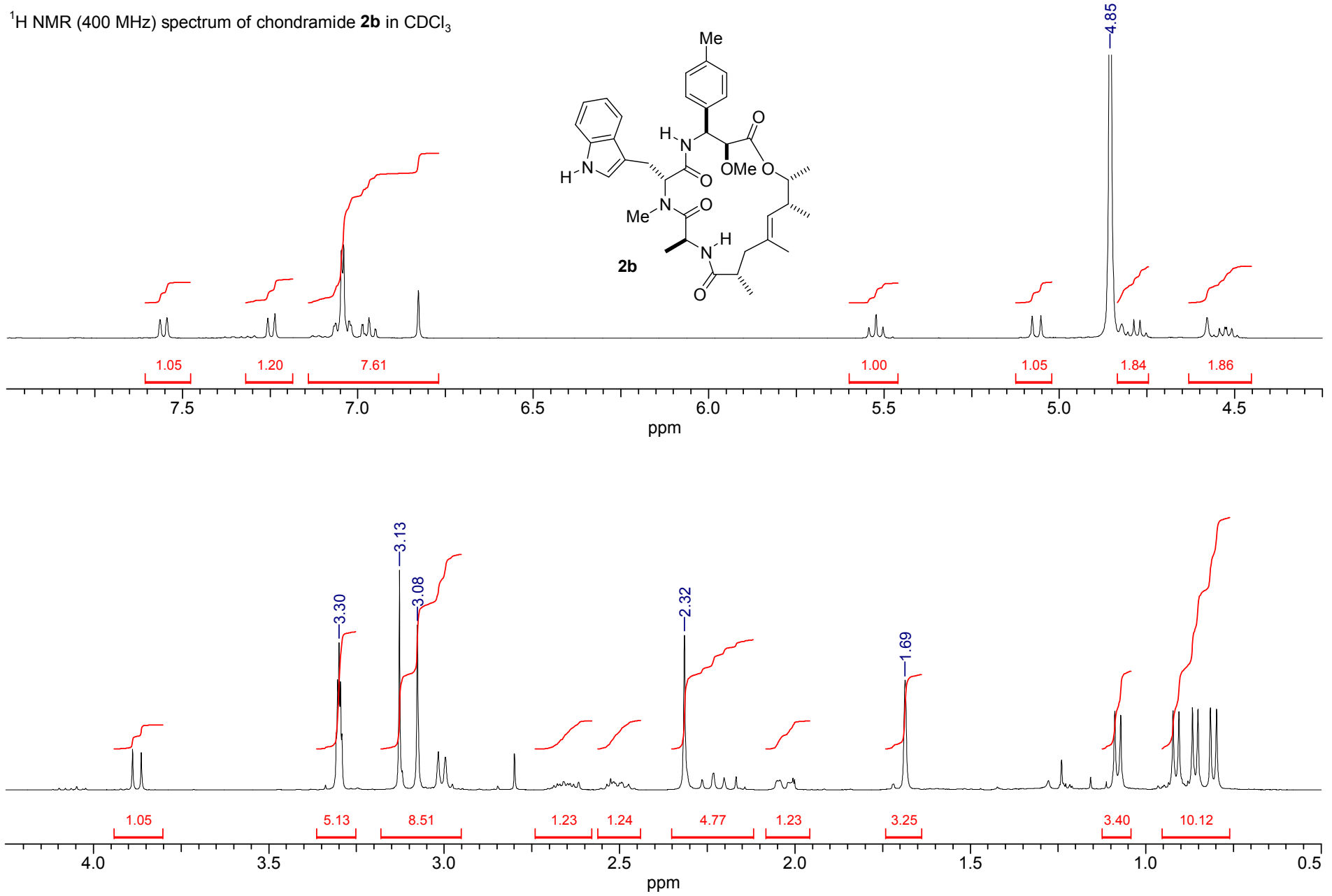
^{13}C NMR (100 MHz) spectrum of depsipeptide **22k** in $CDCl_3$



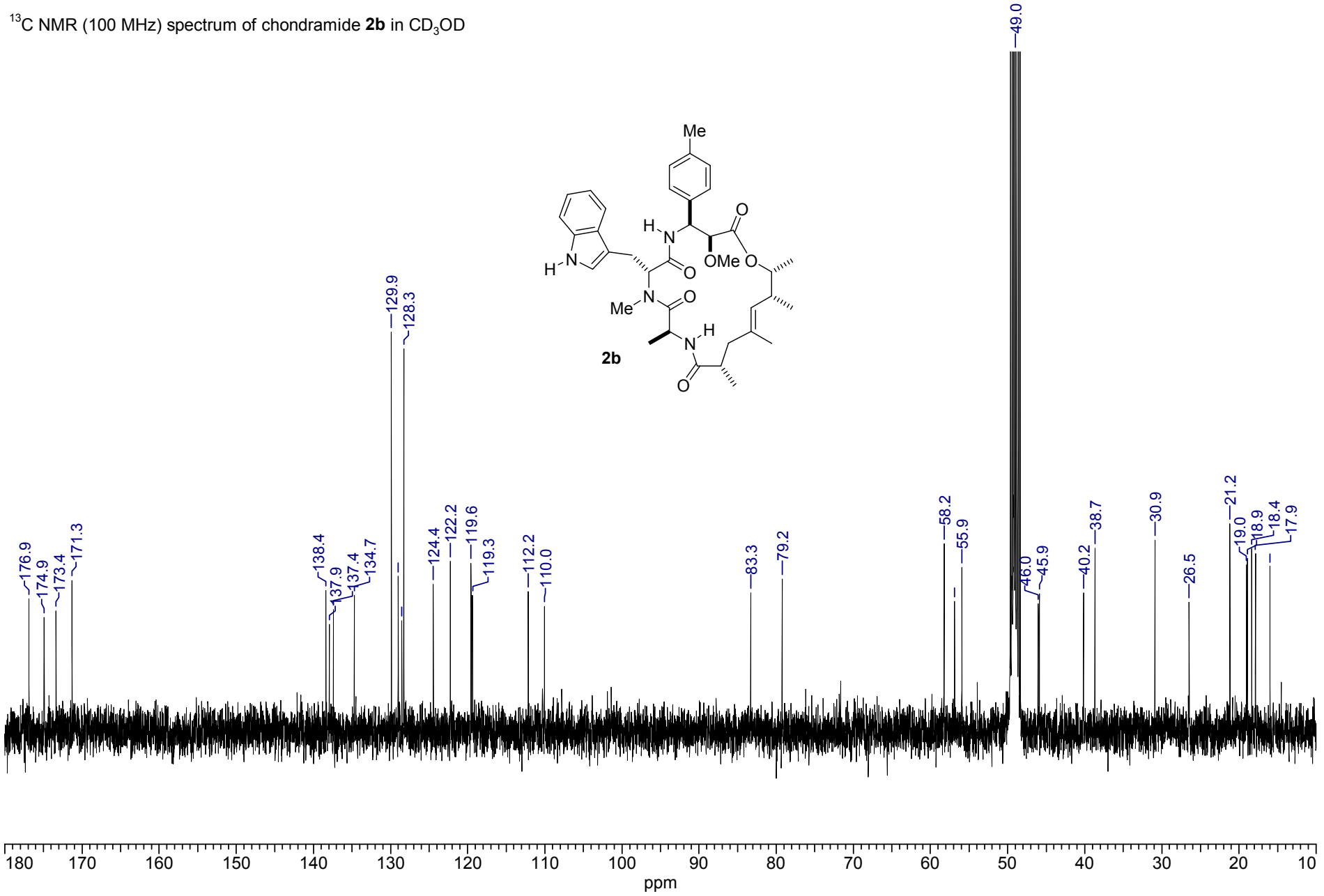
22k



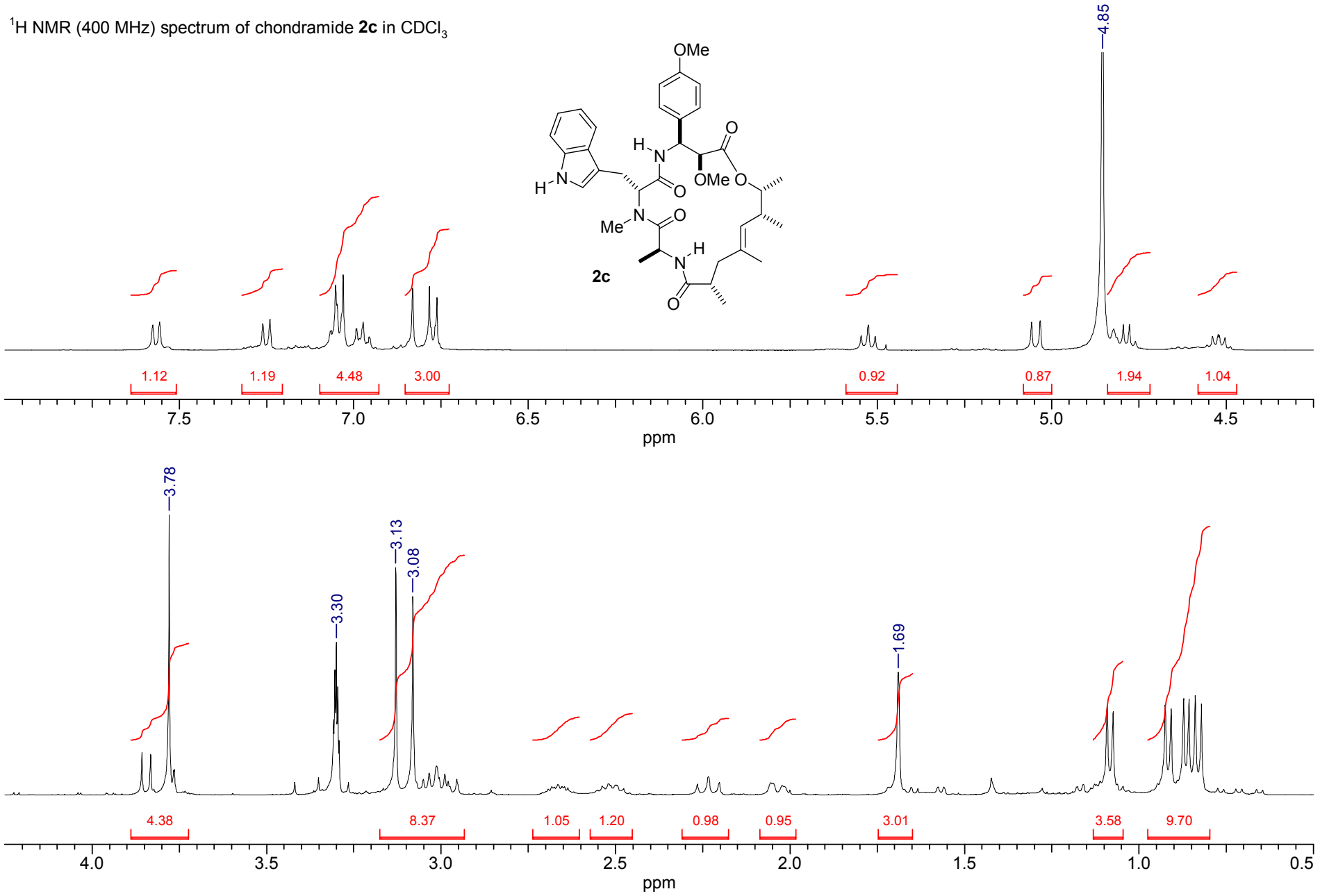
^{1}H NMR (400 MHz) spectrum of chondramide **2b** in $CDCl_3$



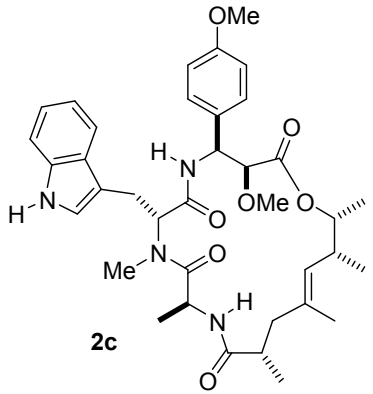
^{13}C NMR (100 MHz) spectrum of chondramide **2b** in CD_3OD



^{1}H NMR (400 MHz) spectrum of chondramide **2c** in $CDCl_3$

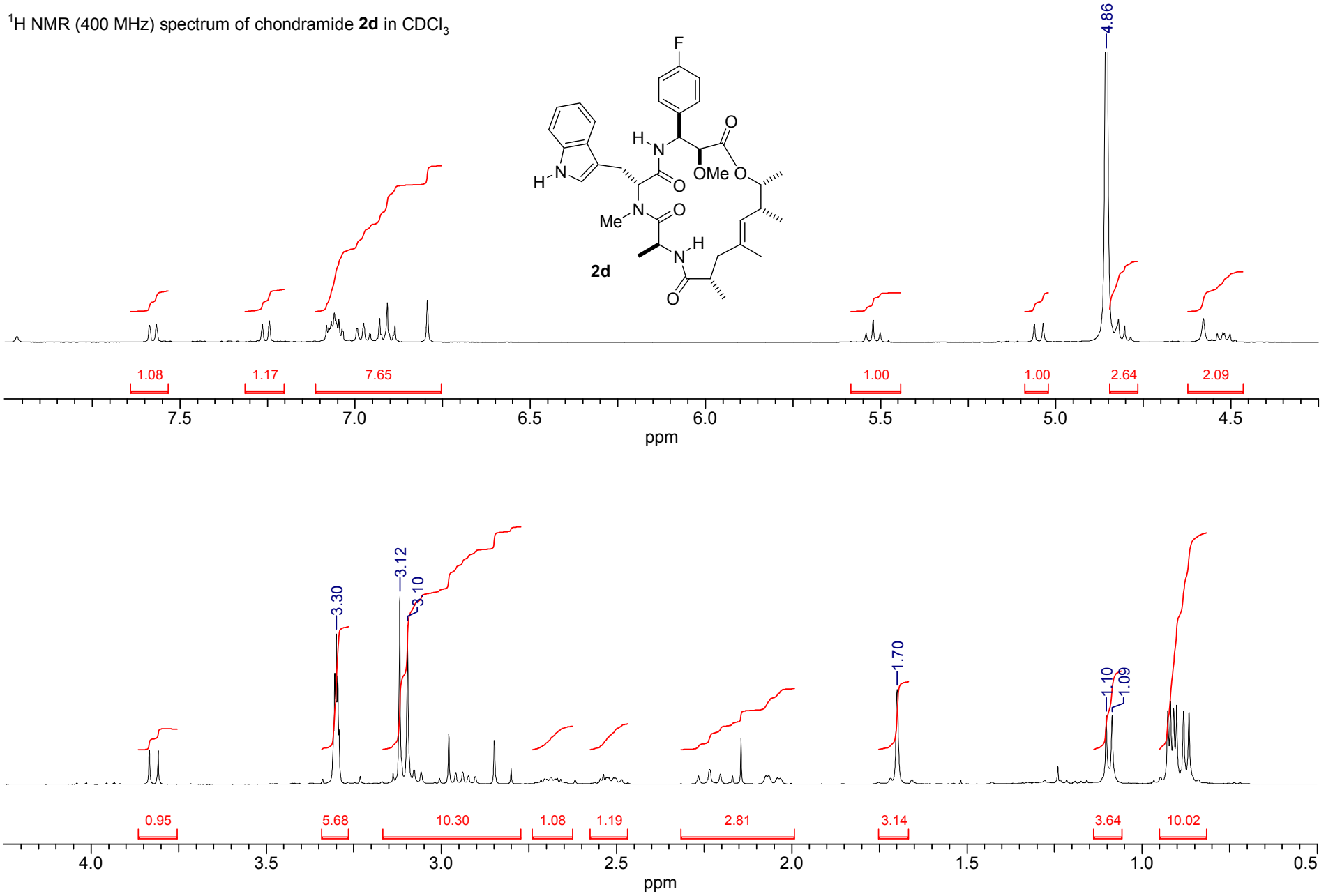


^{13}C NMR (100 MHz) spectrum of chondramide **2c** in CD_3OD

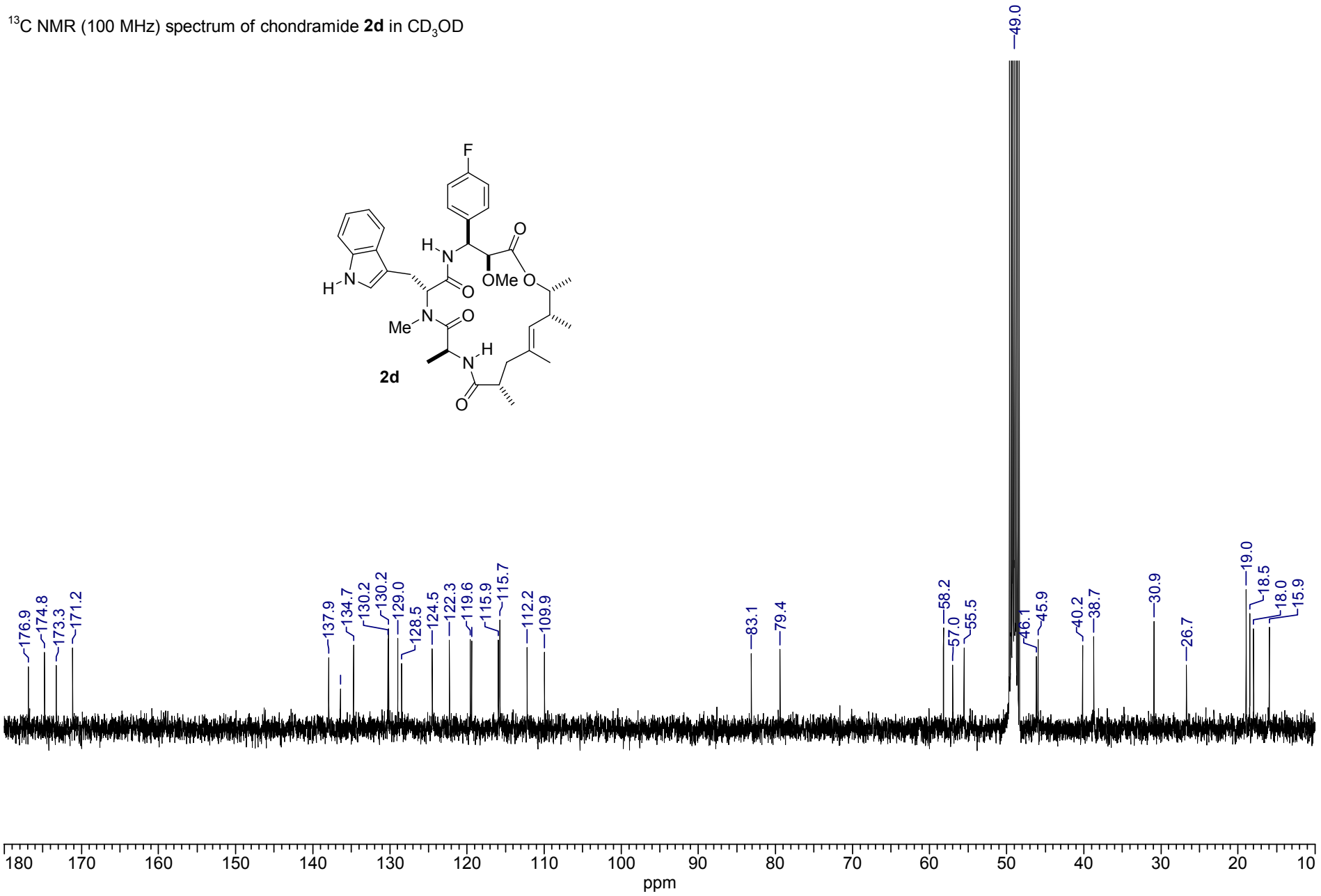


2c

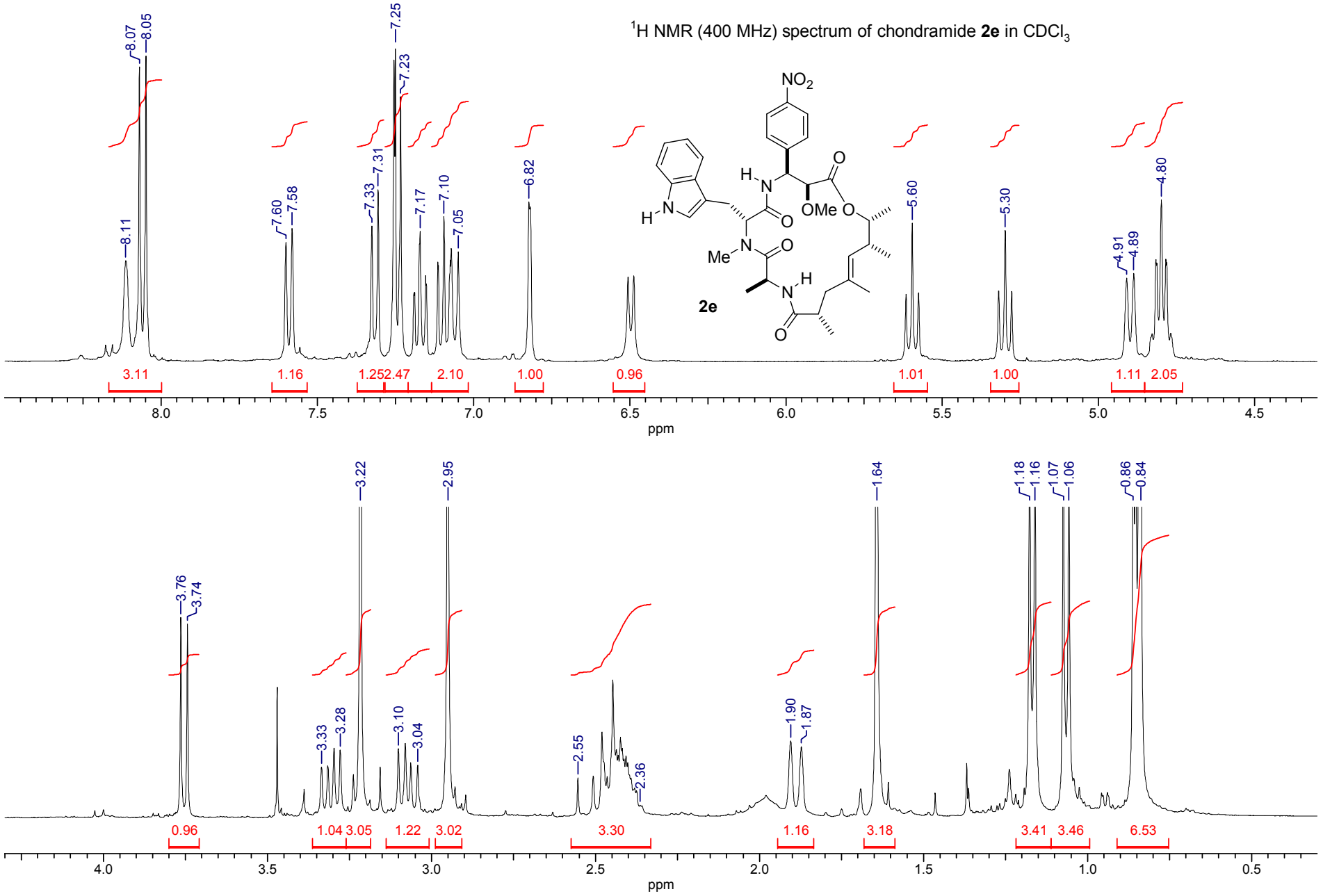
^{1}H NMR (400 MHz) spectrum of chondramide **2d** in $CDCl_3$



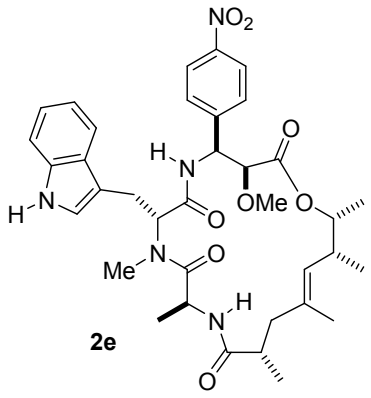
^{13}C NMR (100 MHz) spectrum of chondramide **2d** in CD_3OD



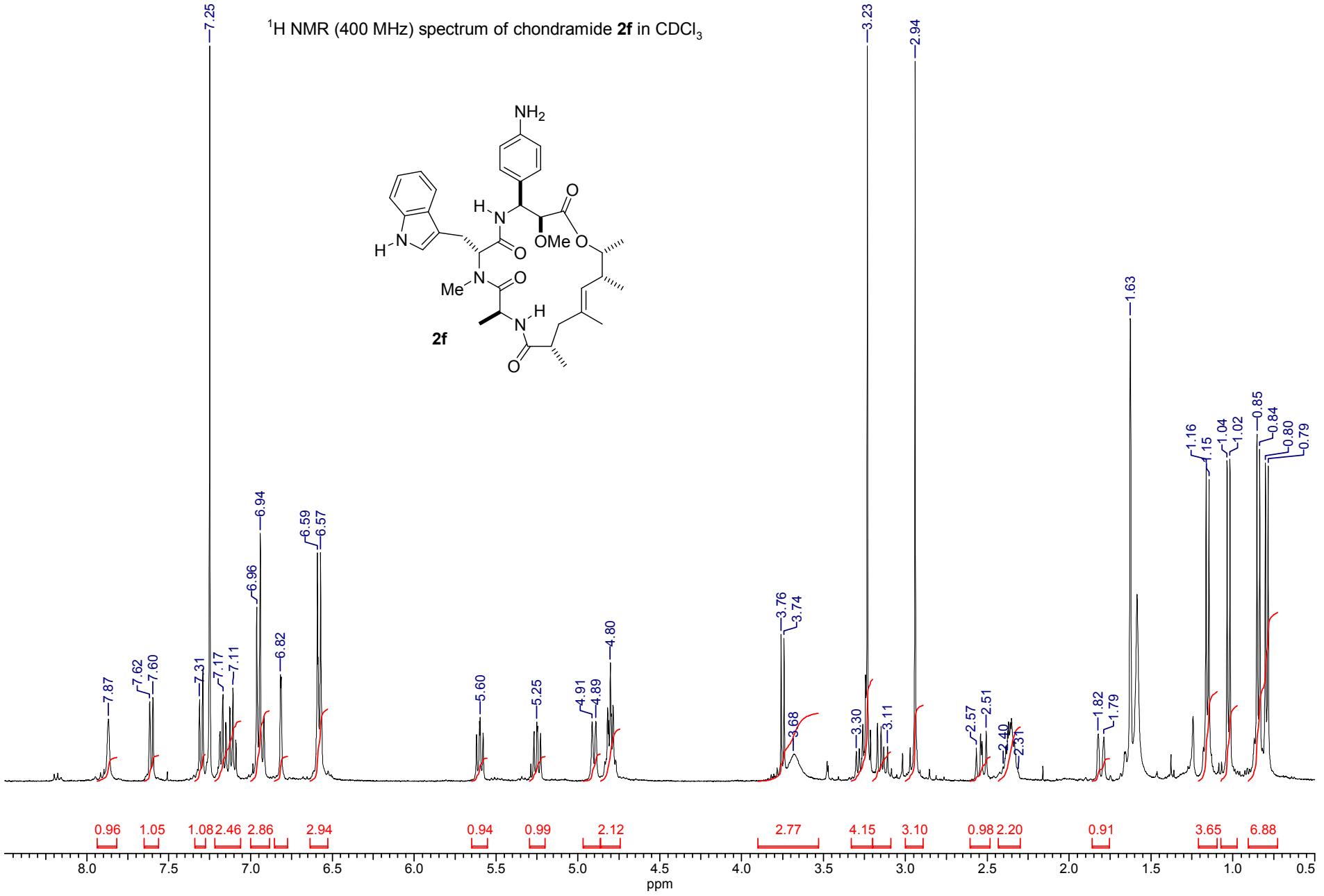
^{1}H NMR (400 MHz) spectrum of chondramide **2e** in $CDCl_3$



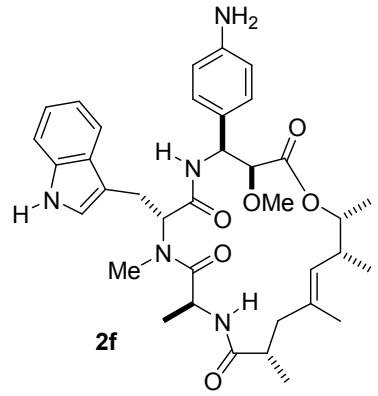
^{13}C NMR (100 MHz) spectrum of chondramide **2e** in $CDCl_3$



2e

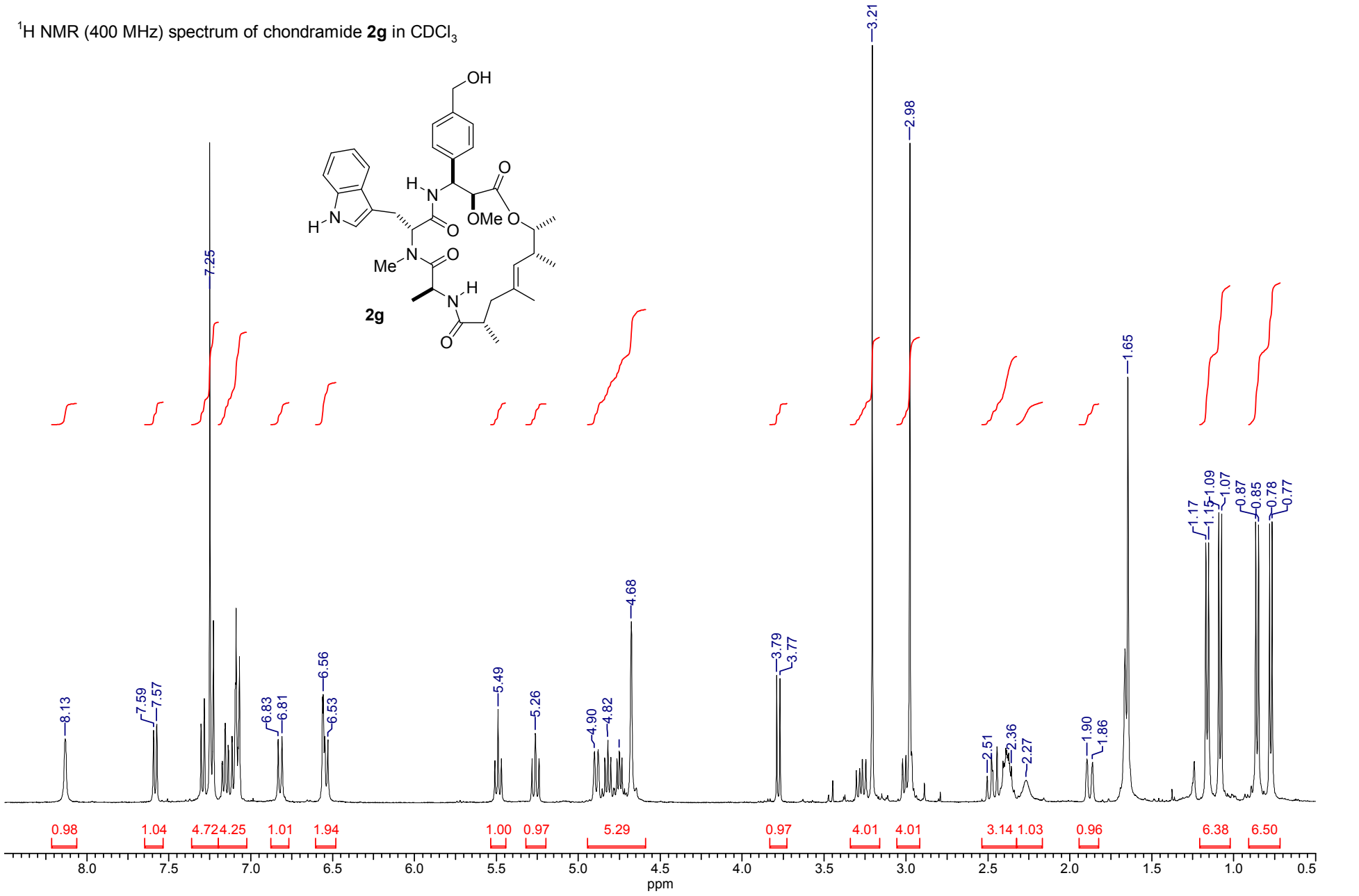

^{1}H NMR (400 MHz) spectrum of chondramide **2f** in $CDCl_3$
2f
7.25
3.23
2.94
1.63
7.87
7.62
7.60
7.31
7.17
7.11
6.96
6.94
6.82
6.59
6.57
5.60
5.25
4.91
4.89
4.80
3.76
3.74
3.68
3.30
3.11
2.57
2.51
2.40
2.31
1.82
1.79
1.16
1.15
1.04
1.02
0.85
0.84
0.80
0.79
0.96
1.05
1.08
2.46
2.86
2.94
0.94
0.99
2.12
2.77
4.15
3.10
0.98
2.20
0.91
3.65
6.88
ppm

^{13}C NMR (100 MHz) spectrum of chondramide **2f** in $CDCl_3$

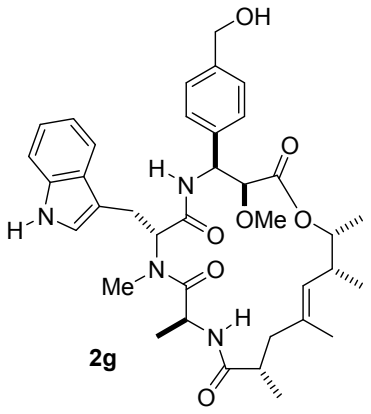


2f

^{1}H NMR (400 MHz) spectrum of chondramide **2g** in $CDCl_3$

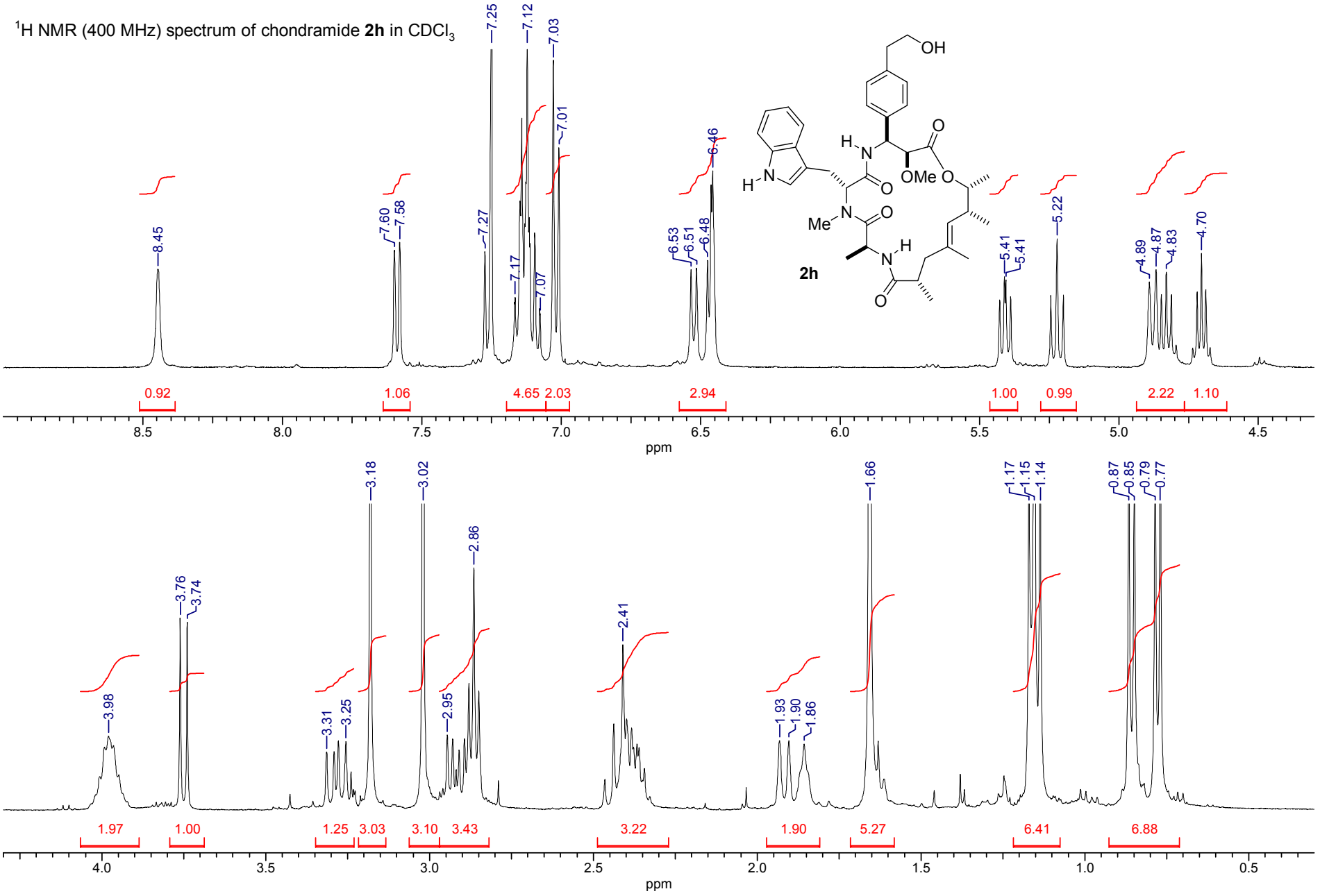


^{13}C NMR (100 MHz) spectrum of chondramide **2g** in $CDCl_3$

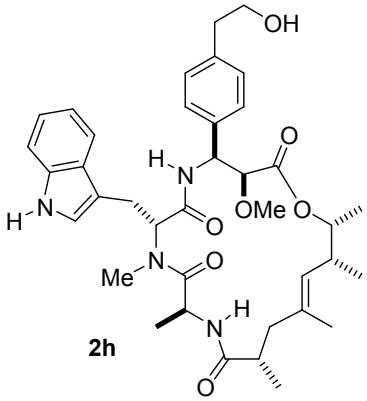


2g

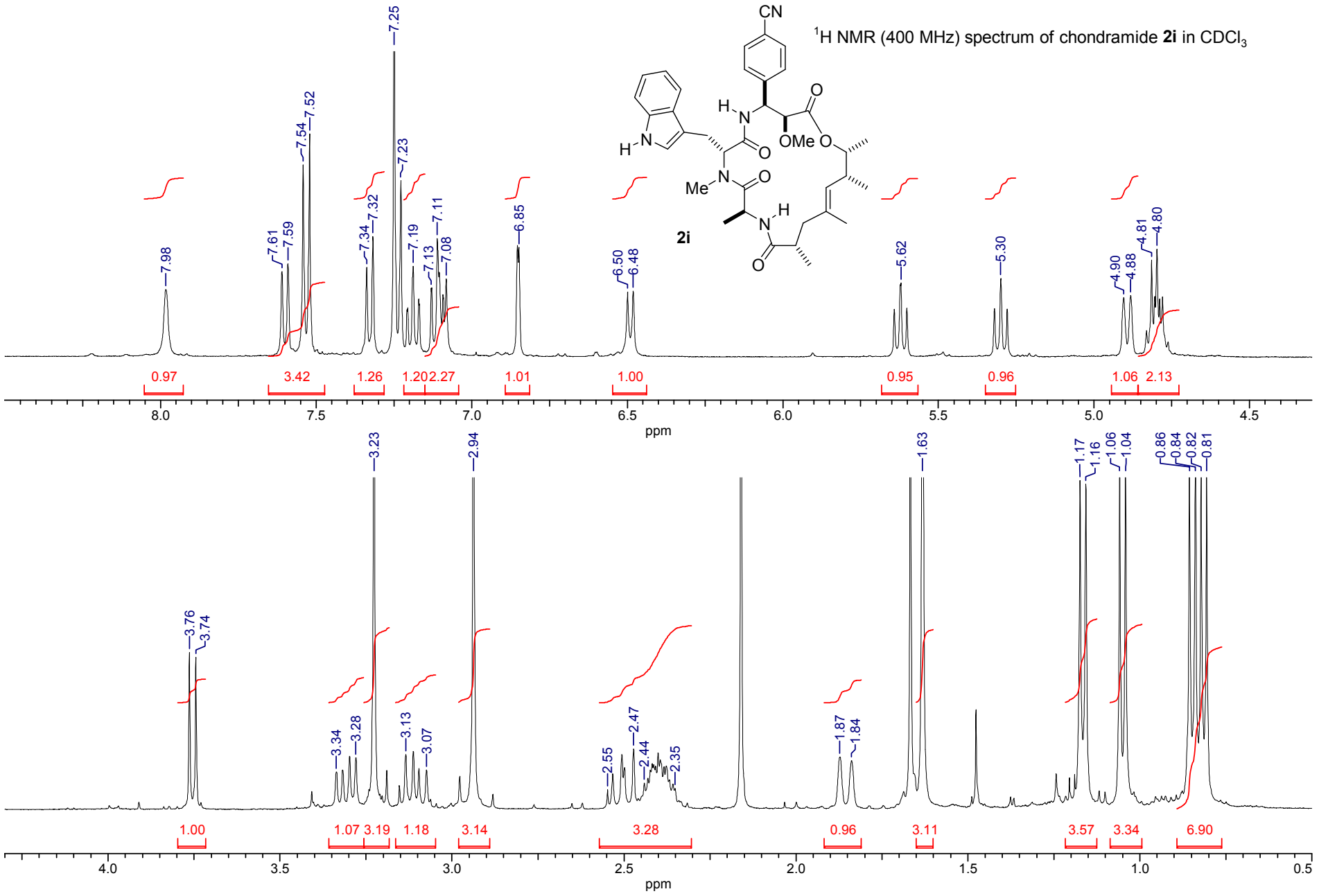
^{1}H NMR (400 MHz) spectrum of chondramide **2h** in $CDCl_3$



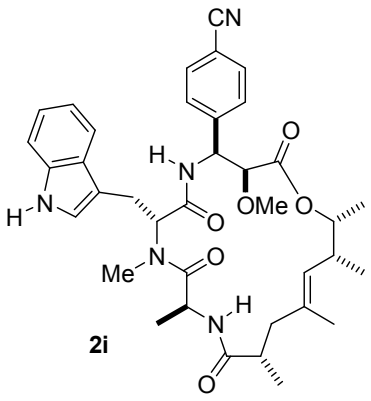
^{13}C NMR (100 MHz) spectrum of chondramide **2h** in $CDCl_3$



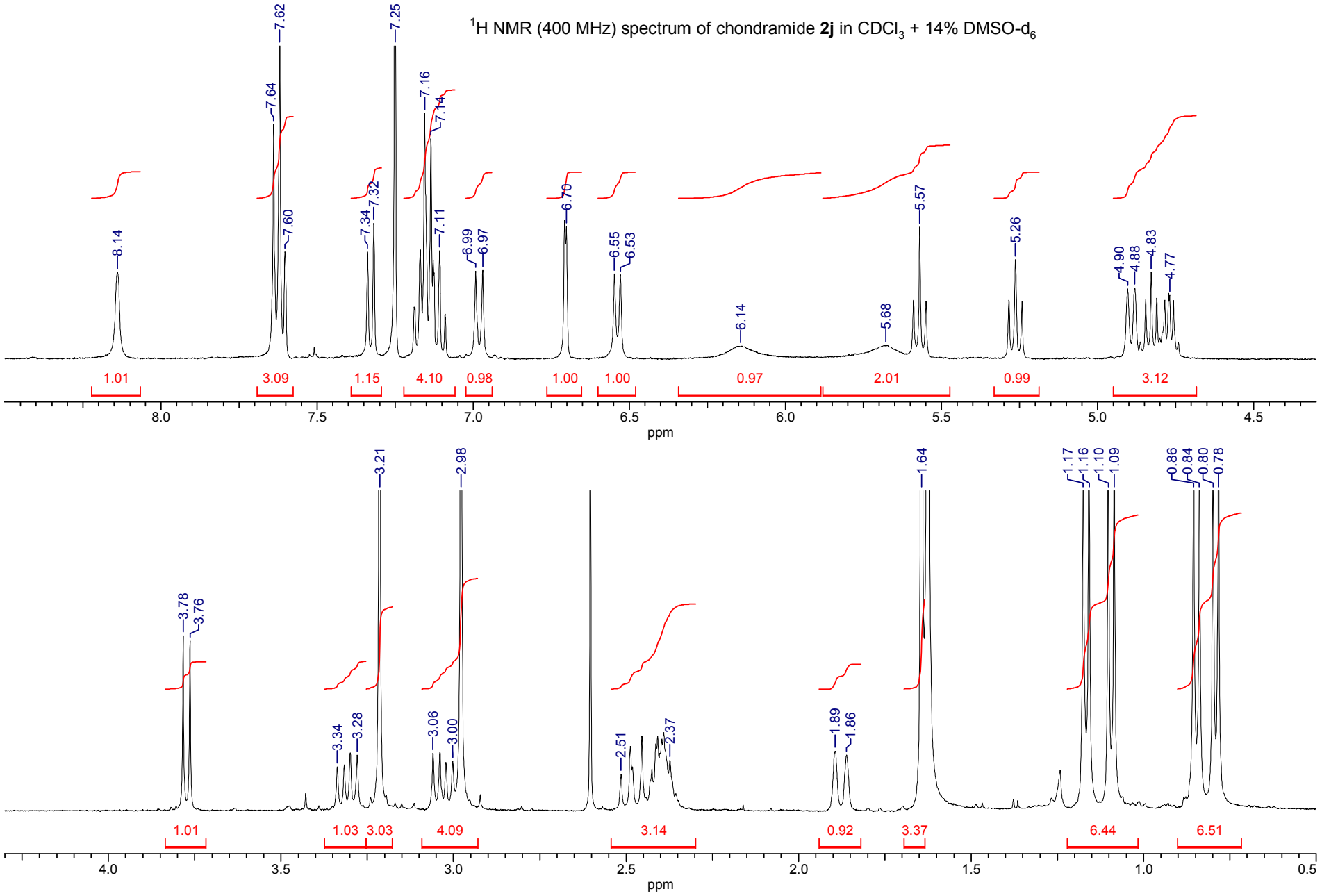
2h


^{1}H NMR (400 MHz) spectrum of chondramide **2i** in $CDCl_3$
2i
7.98
7.61
7.59
7.54
7.52
7.34
7.32
7.25
7.23
7.19
7.13
7.11
7.08
6.85
6.50
6.48
5.62
5.30
4.90
4.88
4.81
4.80
0.97
3.42
1.26
1.20
2.27
1.01
1.00
0.95
0.96
1.06
2.13
ppm
3.76
3.74
3.34
3.28
3.23
3.13
3.07
2.94
2.55
2.47
2.44
2.35
1.87
1.84
1.63
1.17
1.16
1.06
1.04
0.86
0.84
0.82
0.81
1.00
1.07
3.19
1.18
3.14
3.28
0.96
3.11
3.57
3.34
6.90
ppm

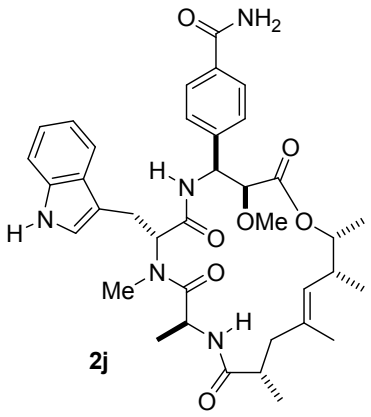
^{13}C NMR (100 MHz) spectrum of chondramide **2i** in $CDCl_3$



2i

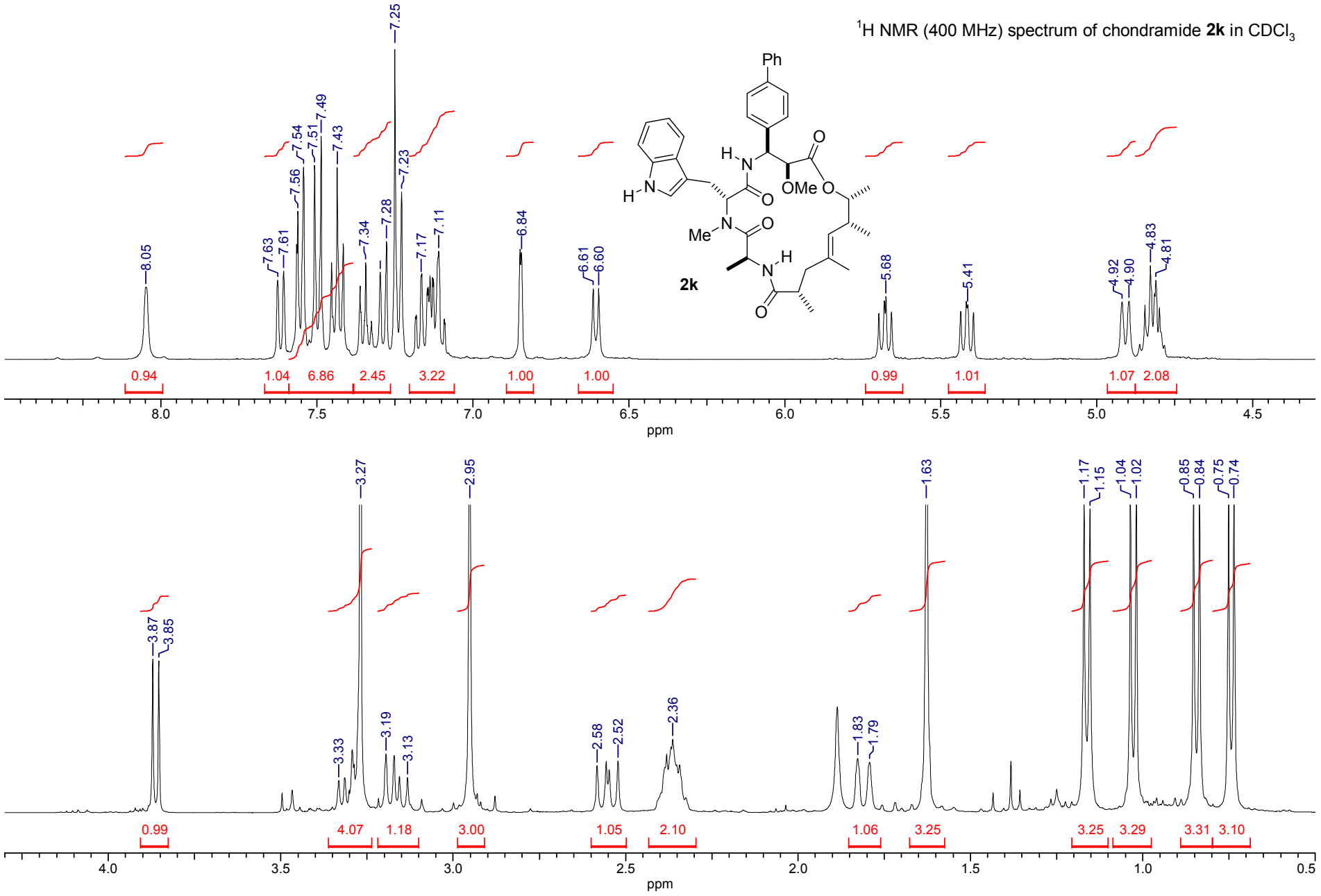

^{1}H NMR (400 MHz) spectrum of chondramide **2j** in $CDCl_3$ + 14% DMSO-d_6
8.14
7.64
7.62
7.60
7.34
7.32
7.25
7.16
7.14
7.11
6.99
6.97
6.70
6.55
6.53
6.14
5.68
5.57
5.26
4.90
4.88
4.83
4.77
1.01
3.09
1.15
4.10
0.98
1.00
1.00
0.97
2.01
0.99
3.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
3.78
3.76
3.34
3.28
3.21
3.06
3.00
2.98
2.51
2.37
1.89
1.86
1.64
1.17
1.16
1.10
1.09
0.86
0.84
0.80
0.78
1.01
1.03
3.03
4.09
3.14
0.92
3.37
6.44
6.51
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

^{13}C NMR (100 MHz) spectrum of chondramide **2j** in $CDCl_3$



2j

^{1}H NMR (400 MHz) spectrum of chondramide **2k** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of chondramide **2k** in $CDCl_3$