

CHEMISTRY

A European Journal

Supporting Information

A Total Synthesis of Salinosporamide A

Léo B. Marx and Jonathan W. Burton*^[a]

chem_201800046_sm_miscellaneous_information.pdf

Experimental Procedures

General Remarks

NMR spectra were recorded on Bruker AV400, AVII500, and DRX500 spectrometers. Proton and carbon chemical shifts (δ_H , δ_C) are quoted in ppm and referenced to tetramethylsilane with residual protonated solvent as internal standard. For chloroform-*d*, solvent residuals are 7.27 ppm and 77.16 ppm for proton and carbon respectively. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and combinations thereof. Coupling constants (*J*) are given in Hz and rounded to nearest 0.1 Hz. For diastereotopic protons, no particular stereochemistry is implied.

Mass spectra (low resolution) were recorded on a Micromass ZMD (ES). High resolution spectra were recorded by the Mass Spectrometry service at the Chemical Research Laboratory, University of Oxford using a Bruker Daltonics microTOF (ES) or a Micromass GCT (FI). *m/z* values are reported in Daltons with their percentage abundance and, where known, the relevant fragment ions in parentheses. High resolution values are calculated to 4 d.p. from the molecular formula, all found values being within 5 ppm tolerance.

Infrared spectra were recorded on Bruker Tensor 27 equipped with a diamond ATR. Absorption maxima (ν_{\max}) are described as s (strong), m (medium), w (weak), and br (broad) and are quoted in wavenumbers (cm^{-1}).

Optical rotations were recorded using an Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (l) using the sodium D line (589 nm).

HPLC analysis was undertaken on an Agilent 1200 with DAD, equipped with ChiralPak® AD-H column.

TLC was performed on Merck DC-Alufolien 60 F₂₅₄ 0.2 mm precoated plates and visualised using an acidic vanillin or basic potassium permanganate dip. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography was performed on Merck 60 silica (particle size 40–63 μm , pore diameter 60 Å) and the solvent system used is recorded in parentheses.

All non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen and employing standard techniques for handling air-sensitive materials. Solvents and commercially available reagents were dried and purified before use, as appropriate. In particular DCM and THF were distilled from CaH₂ and stored over 3 Å molecular sieves. ‘PE’ refers to the fraction of light petroleum ether boiling in the range 40–60 °C unless otherwise stated. All water used experimentally was distilled. pH 2 sulfate buffer was prepared by dissolving NaHSO₄ (213 g, 1.50 mol) and conc. H₂SO₄ (28.0 mL, 0.500 mol) in water (1.00 L). pH 3 citric acid buffer was prepared by dissolving citric acid (192 g, 1.00 mol) and NaOH (20.0 g, 0.500 mol) in water (2.00 L).

Compounds not explicitly numbered in the main text are denoted **S1**, **S2**, etc. Novel compounds are denoted by the use of *italics*.

Literature compounds. The following compounds were prepared according to literature methods: (*R*)-4-Benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one¹ di-*tert*-butyl 2-((4-methoxybenzyl)amino)malonate,¹ (dibenzy 2-(hydroxyimino)malonate,² dimethyl 2-aminomalonate³, (*E*)-1-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3*a*,6-methanobenzo[*c*]isothiazol-1-yl)but-2-en-1-one.⁴

(-)-Salinosporamide A - Synthesis and Compound Characterisation

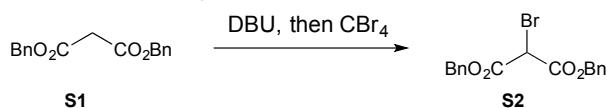
General Procedure 1: Amide coupling with HATU

To a solution of acid (1.00 eq), free amine or amine-HCl salt (1.15 eq.) and DIPEA (2.00 eq. for free amine or 3.00 eq. for amine-HCl) in dry DMF (5 mL/mmol of acid) at 0 °C, was added HATU (1.05 eq.) portionwise (100 mg per portion added every 20 seconds). The reaction was stirred at 0 °C under nitrogen for 5 min and then for two hours at 22 °C. The reaction was quenched with pH 2 sulfate buffer (0.5 mL/mmol of acid). The residue was diluted with EtOAc (15 mL/mmol of acid) and the organic phase was washed with a solution of pH 2 sulfate buffer/H₂O (1:1, 20 mL/mmol of acid) followed by a saturated aqueous solution of NaHCO₃ (10 mL/mmol of acid). The organic layer was dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography using an PE:EtOAc solvent system, which gave an R_f for the product between 0.3 and 0.5.

General Procedure 2: Oxidative elimination of benzeneselenenic acid

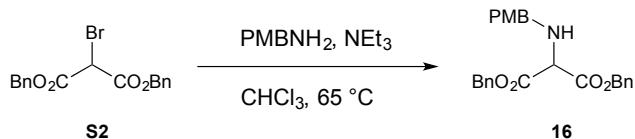
According to the modified procedure of Kocienski *et al.*,⁵ NaIO₄ (3.00 eq.) was added to a stirred mixture of NaHCO₃ (3.00 eq.) and amidomalonate (200 mg, 0.410 mmol) in 1:1:1 MeOH/THF/H₂O (30 mL/mmol of amidomalonate) at 22 °C under air and stirred for a further 15 min. H₂O (50 mL/mmol amidomalonate) and DCM (60 mL/mmol amidomalonate) were added and the mixture was stirred vigorously before being filtered through a Celite™ pad, which was eluted with DCM (2 × 25 mL/mmol amidomalonate). The aqueous layer was extracted with DCM (2 × 25 mL/mmol amidomalonate), the combined organic extracts were dried (Na₂SO₄), filtered, and the solvent was quickly removed *in vacuo*. The crude selenoxide was dissolved in CHCl₃ (20 mL/mmol amidomalonate) and heated at 75 °C for 25 min. The reaction mixture was then cooled to 22 °C and the solvent was removed *in vacuo* to give the crude product.

Dibenzyl 2-bromomalonate S2



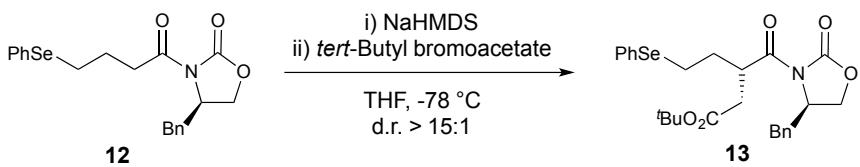
According to the modified procedure of Perreault *et al.*,⁶ DBU (2.97 g, 19.5 mmol) was slowly added to dibenzyl malonate **S1** (6.54 g, 19.5 mmol) in dry THF (160 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and was then cooled to -78 °C. CBr₄ (6.46 g, 19.5 mmol) was then added in one portion. The reaction mixture was stirred at -78 °C for 6 h and was quenched by slow addition of an aqueous saturated solution of NH₄Cl (60 mL) and water (20 mL). The mixture was warmed to 22 °C, the organic layer was separated and washed with brine (50 mL). The combined aqueous layers were extracted with DCM (2 × 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (14:1 PE:EtOAc), which gave the title compound **S2** as a colourless oil (5.30 g, 14.6 mmol, 75%). R_f 0.63 (9:1 PE:EtOAc); δ_H (400 MHz, CDCl₃) 7.39–7.31 (m, 10H, ArH), 5.24 (s, 4H, CH₂Ph), 4.94 (1H, s, CHBr); δ_C (100 MHz, CDCl₃) 164.4 (2C=O), 134.6 (Ar), 128.7 (Ar), 128.4 (Ar), 68.8 (CH₂Ph), 42.4 (CHBr) – one accidental equivalence in aromatic region; ν_{max} 1739 (s, C=O), 1230 (s), 1136 (s, C-O), 738 (m, Ar), 695 (w); m/z (ESI⁺): 385 and 387; ([M+Na]⁺, 100%); HRMS found 385.0041 and 387.0022, [C₁₇H₁₅BrNaO₄]⁺ requires 385.0046 and 387.0026. Data are consistent with literature values.⁷

Dibenzyl 2-((4-methoxybenzyl)amino)malonate 16



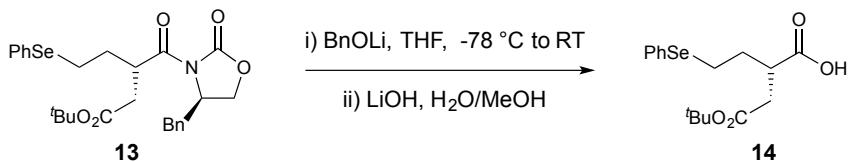
According to the modified procedure of Hess *et al.*,⁸ a mixture of dibenzyl 2-bromomalonate **S2** (2.99 g, 8.23 mmol), NEt₃ (2.30 mL, 16.5 mmol) and 4-methoxybenzylamine (2.10 mL, 16.5 mmol) was heated under reflux (65 °C) in CHCl₃ (80 mL) for 90 min. The reaction mixture was cooled to 22 °C, and DCM (40 mL) and H₂O (80 mL) were added. The aqueous layer was extracted with more DCM (2 × 40 mL). The combined organic extracts were dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (7:1 PE:EtOAc), which gave the title compound **16** as a yellow oil (1.05 g, 2.51 mmol, 30%) containing a minor impurity. **R**_f 0.51 (9:1 PE:EtOAc); **δ**_H (400 MHz, CDCl₃) 7.40–7.26 (10H, m, ArH), 7.23–7.18 (2H, m, ArH), 6.85–6.82 (2H, m, ArH), 5.17 (s, 4H, CH₂Ph), 4.70 (1H, s, NH), 4.17 (1H, s, CH), 3.80 (3H, s, CH₃), 3.74 (2H, s, CH₂Ar); **δ**_C (100 MHz, CDCl₃) 168.4 (2 × C=O), 159.0 (Ar), 135.2 (Ar), 129.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 127.1 (Ar), 113.9 (Ar), 67.5 (CH₂Ph), 64.0 (s, CH), 55.4 (CH₂Ar), 51.0 (CH₃); **v**_{max} 2955 (w, C-H), 1735 (s, C=O), 1512 (m), 1247 (s), 1213 (m), 1173 (m), 1031 (w), 738 (m), 687 (m); **m/z** (ESI⁺) 861 ([2M+Na]⁺, 100%), 420 ([M+H]⁺, 90%); HRMS found 442.1610, [C₂₅H₂₆NNaO₅]⁺ requires 442.1625.

(R)-tert-Butyl 3-((R)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-(phenylselanyl)pentanoate
13



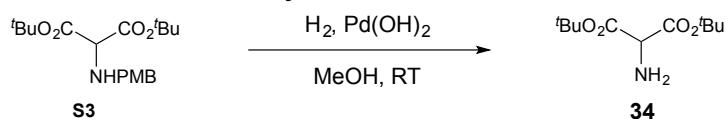
To a stirred solution of oxazolidinone **12**¹ (7.32 g, 18.2 mmol) in THF (180 mL) at -78 °C, was added NaHMDS in THF (2.0 M, 12.8 mL, 25.5 mmol) dropwise over 10 min. After 10 min, *tert*-butyl bromoacetate (8.06 mL, 54.6 mmol) was added dropwise over 10 min and the reaction was stirred for a further 45 min. A saturated aqueous solution of NaHCO₃ (200 mL) was added, and the reaction was warmed to 22 °C. The mixture was extracted with EtOAc (1×200 mL, then 2×100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (7:1 PE:EtOAc), which gave the title compound **13** as a colourless oil (8.01 g, 15.5 mmol, 85%). **R**_f 0.44 (7:1 PE:EtOAc); **δ**_H (400 MHz, CDCl₃) 7.50–7.48 (2H, m, ArH), 7.37–7.31 (2H, m, ArH), 7.30–7.20 (6H, m, ArH), 4.65–4.61 (1H, m, NCHBn), 4.27–4.21 (1H, m, HC(CO)N), 4.16–4.12 (2H, m, CO₂CHH), 3.32 (1H, dd, *J* = 13.4, 3.5, CH/HPh), 2.90–2.96 (2H, m, PhSeCH₂), 2.80 (1H, dd, *J* = 16.5, 10.5, CHHCO₂^tBu), 2.74 (1H, dd, *J* = 13.4, 9.9, CHHPh), 2.48 (1H, dd, *J* = 16.5, 4.6, CHHCO₂^tBu), 2.12–2.08 (1H, m, PhSeCH₂CHH), 1.88 (1H, dddd, *J* = 13.6, 9.6, 6.7, 6.7, PhSeCH₂CHH), 1.43 (9H, s, OC(CH₃)₃); **δ**_C (100 MHz, CDCl₃) 174.9 (C=O), 171.0 (C=O ester), 153.1 (C=O oxazolidinone), 135.7 (Ar), 132.7 (Ar), 129.8 (Ar), 129.6 (Ar), 129.2 (Ar), 129.0 (Ar), 127.4 (Ar), 127.1 (Ar), 81.1 (OC(CH₃)₃), 66.1 (CO₂CH₂), 55.6 (NCH), 40.0 (CHC=O), 37.6 (CH₂Ph), 37.0 (CH₂CO₂^tBu), 32.5 (PhSeCH₂CH₂), 28.2 (OC(CH₃)₃), 24.4 (PhSeCH₂); **v**_{max} 2978 (w, C-H), 1779 (s, C=O oxazolidinone), 1725 (m, C=O ester), 1695 (m, C=O), 1391 (m), 1156 (m, C-O), 737.5 (m) (Ar); **m/z** (ESI⁺) 1057 ([2M+Na]⁺, 100%), 540 ([M+Na]⁺, 55%); HRMS found 540.1258, [C₂₆H₃₁NNaO₅⁸⁰Se]⁺ requires 540.1261; [α]_D²⁰ -36.5 (c = 1.00, CHCl₃).

(R)-4-(tert-Butoxy)-4-oxo-2-(2-(phenylselanyl)ethyl)butanoic acid 14



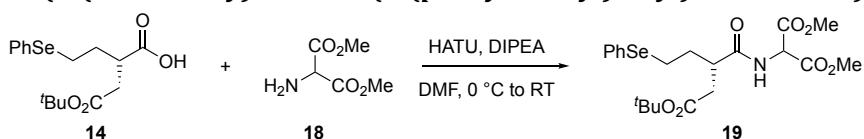
To a nitrogen sparged solution of BnOH (1.61 mL, 15.6 mmol) in THF (160 mL) at 0 °C was added dropwise *n*-BuLi solution in hexane (2.5 M, 5.00 mL, 12.4 mmol). The mixture was stirred at 0 °C for 45 min and then cooled to -78 °C. A solution of oxazolidinone **13** (5.65 g, 10.4 mmol) in THF (40 mL) was added dropwise at -60 °C. The reaction mixture was then warmed to 22 °C over 3 h. A solution of LiOH (2.18 g, 51.9 mmol) in 1:1 H₂O/MeOH (160 mL) was added at 0 °C *via* cannula over 5 min. The reaction mixture was stirred at 22 °C for 16 h. The solvent was removed *in vacuo*, and then an aqueous solution of pH 2 sulfate buffer (100 mL) was slowly added at 0 °C. The mixture was treated with concentrated HCl dropwise until pH 2 was reached. The white emulsion was extracted with EtOAc (3 × 125mL). The combined organic extracts were dried (Na₂SO₄), filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (1:2 PE:EtOAc), which gave a mixture of benzyl alcohol and the desired product. The mixture was co-evaporated several times with H₂O/MeOH (1:1, 5 × 70 mL) and gave the acid **14** as a pale yellow oil (3.16 g, 8.84 mmol, 85%). **R**_f 0.19 (99:1 DCM:AcOH); **δ**_H (400 MHz, CDCl₃) 7.52–7.46 (2H m, ArH), 7.30–7.22 (3H, m, ArH), 2.99–2.91 (3H, m, PhSeCHH and CHCO₂H), 2.61 (1H, dd, *J* = 16.5, 5.6, CHHCO₂^tBu), 2.40 (1H, dd, *J* = 16.5, 8.6, CHHCO₂^tBu), 2.11–2.05 (1H, m, PhSeCH₂CHH), 1.91–1.85 (1H, m, PhSeCH₂CHH), 1.42, (9H, s, OC(CH₃)₃); **δ**_C (100 MHz, CDCl₃) 180.5 (C=O acid), 170.7 (C=O ester), 132.9 (Ar), 129.3 (2 × Ar), 127.2 (Ar), 81.4 (OC(CH₃)₃), 41.5 (CHCO₂H), 36.9 (CH₂CO₂^tBu), 32.0 (PhSeCH₂CH₂), 28.1 (OC(CH₃)₃), 24.7 (PhSeCH₂); **v**_{max} 3500–2500 (br, OH), 2978 (br, C-H), 1729 (s, C=O ester), 1707 (s, C=O acid), 1368 (s), 1154s (C-O), 737 (w, Ar); **m/z** (ESI⁺) 357 ([M-H]⁺, 100%); HRMS found 381.0569 ([M+Na]⁺), [C₁₆H₂₂NaO₄⁸⁰Se]⁺ requires 381.0576; **[α**_D²⁰ - 14.9 (*c* = 1.00 in CHCl₃).

Di-tert-butyl 2-aminomalonate 34



To an N₂ purged solution of PMB protected amine **S3**¹ (10.4 g, 29.5 mmol) in MeOH (120 mL) was added Pd(OH)₂ (20% on activated carbon, 1.00 g). The atmosphere was then replaced with H₂. Vigorous stirring was maintained for 12 h under H₂ (balloon pressure). The reaction was then placed under N₂ atmosphere and the mixture was filtered through a Celite™ pad, which was further eluted with MeOH (2×30 mL). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (2:1 PE:Et₂O 3CV, then Et₂O 3CV), which gave the title compound **34** (6.40 g, 26.1 mmol, 89%) as a colourless oil. R_f 0.65 (3:1 PE:EtOAc); δ _H (400 MHz, CDCl₃) 3.94 (s, 1H, CH), 1.81 (2H, br, NH₂), 1.46 (18H, s, OC(CH₃)₃); δ _C (100 MHz, CDCl₃) 169.1 (C=O), 82.4 (C(CH₃)₃), 60.1 (CH), 28.0 (OC(CH₃)₃); ν _{max} 2979 (w, C-H), 1732 (s, C=O), 1142 (s, C-O), 848 (w); **m/z** (ESI⁺) 254 ([M+Na]⁺, 100%); HRMS found 254.1363, [C₁₁H₁₁NNaO₄]⁺ requires 254.1363.

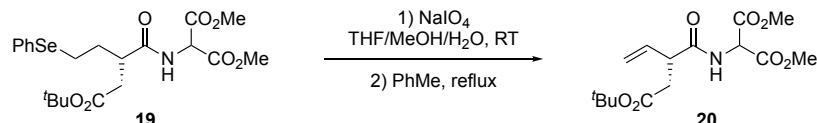
(R)-Dimethyl 2-(4-(tert-butoxy)-4-oxo-2-(phenylselanyl)ethyl)butanamido)malonate 19



The title compound was prepared from acid **14** (680 mg, 1.80 mmol) and aminomalonate **18** (336 mg, 3.81 mmol) according to General Procedure 1. The crude product was purified by flash column

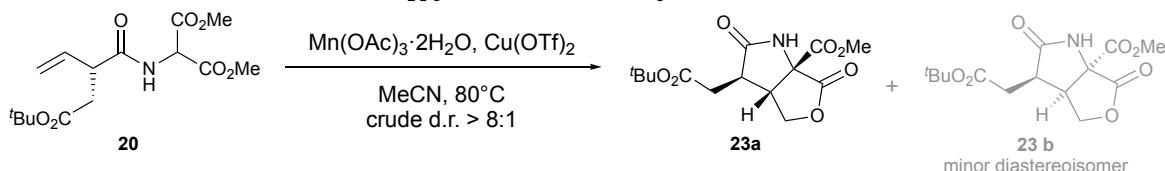
chromatography (3:1 PE:EtOAc), which gave amidomalonate **19** (775 mg, 1.59 mmol, 84%) as a colourless oil. R_f 0.67 (7:3 PE:EtOAc); δ_H (400 MHz, CDCl₃) 7.53–7.48 (2H, m, ArH), 7.30–7.20 (3H, m, ArH), 6.88 (1H, d, J = 6.6, NH), 5.15 (1H, d, J = 6.6, NCH), 3.81 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 3.05–2.82 (3H, m, PhSeCH₂ and HC(CO)N), 2.63 (1H, dd, J = 16.8, 9.1, CHHCO₂^tBu), 2.30 (1H, dd, J = 16.8, 5.1, CHHCO₂^tBu), 2.08 (1H, dddd, J = 13.5, 8.6, 8.6, 5.1, PhSeCH₂CHH), 1.75 (1H, dddd, J = 13.5, 8.1, 8.1, 5.1, PhSeCH₂CHH), 1.40 (9H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 173.8 (C=O), 171.1 (C=O), 166.6 (C=O), 166.4 (C=O), 132.8 (Ar), 129.7 (Ar), 129.2 (Ar), 127.1 (Ar), 81.2 (OC(CH₃)₃), 56.4 (NCH), 53.6 (OCH₃), 53.5 (OCH₃), 41.9 (CH), 37.9 (CH₂CO₂^tBu), 32.4 (PhSeCH₂CH₂), 28.1 (OC(CH₃)₃), 24.9 (PhSeCH₂); ν_{max} 3326 (br, N-H), 2971 (w, C-H), 1745 (s, C=O), 1680 (m, C=O), 1157 (s, C-O), 739 (w, Ar); m/z (ESI+) 510 ([M+Na]⁺, 100%); HRMS found 510.1010, [C₂₁H₂₉NNaO₇Se]⁺ requires 510.1003; $[\alpha]_D^{20}$ -33.3 (c = 1.00, CHCl₃).

(R)-Dimethyl 2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)malonate **20**



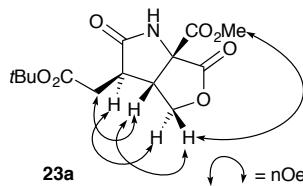
According to General Procedure 2, amidomalonate **19** (200 mg, 0.410 mmol) was treated with NaIO₄ and NaHCO₃ and finally heated under reflux in PhMe (instead of CHCl₃) for 45 min, which after flash column chromatography (3:1 PE:EtOAc) gave alkene **20** (116 mg, 0.352 mmol, 79%) as a colourless oil. R_f 0.61 (7:3 PE:EtOAc); δ_H (400 MHz, CDCl₃) 6.77 (d, J = 6.7, NH), 5.87 (1H, ddd, J = 17.1, 10.2, 7.5, CH=CHH), 5.32 (1H, dd, J = 17.1, 1.0, CH=CHH), 5.27 (1H, dd, J = 10.2, 1.0, CH=CHH), 5.16 (1H, d, J = 6.7, NCH), 3.81 (6H, s, 2 x OCH₃), 3.43 (1H, ddd, J = 7.5, 7.5, 7.5 Hz, HC(CO)N), 2.80 (1H, dd, J = 16.5, 7.5, CHHCO₂^tBu), 2.45 (1H, dd, J = 16.5, 7.5, CHHCO₂^tBu), 1.42 (9H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 171.9 (C=O), 170.9 (C=O), 166.7 (C=O), 166.6 (C=O), 135.0 (CH=CH₂), 119.4 (CH=CH₂), 81.0 (OC(CH₃)₃), 56.4 (NCH), 53.5 (2 x OCH₃), 46.9 (HC(CO)N), 37.1 (CH₂CO₂^tBu), 28.1 (OC(CH₃)₃); ν_{max} 3328 (br, N-H), 2979 (w, C-H), 1733 (C=O esters), 1684m (C=O amide), 1157 (s, C-O); m/z (ESI⁺) 352 ([M+Na]⁺, 100%); HRMS found 352.1358, [C₁₅H₂₃NNaO₇]⁺ requires 352.1367; $[\alpha]_D^{20}$ -42.9 (c = 1.00, CHCl₃).

(3*R*,3*aR*,6*aR*)-Methyl 3-(2-(tert-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-b]pyrrole-6*a*-carboxylate **23a**

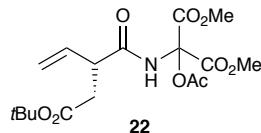


A solution of (*R*)-dimethyl 2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)malonate (211 mg, 0.610 mmol) **20** in nitrogen sparged MeCN (8 + 1 mL rinse) was added to Mn(OAc)₃·2H₂O (327 mg, 1.22 mmol) and Cu(OTf)₂ (131 mg, 0.610 mmol) under argon at 80 °C. The reaction mixture was stirred for 4 h, and was then cooled to 22 °C. The mixture was filtered through a silica pad eluted with EtOAc. The solvent was then evaporated and the residue was purified by flash column chromatography (3:7 PE:EtOAc, then EtOAc) which gave the title compound as a white solid (0.295 mmol, 92.2 mg, 48%) and the two by-products described below. The ¹H NMR analysis of the crude of the reaction indicated the presence of the minor diastereoisomer **23b** (d.r. > 8:1), which could not be isolated in a pure form after flash column chromatography. Characterisation is given for the major diastereoisomer **23a**. R_f 0.69 (Et₂O); m.p. 85–87 °C; δ_H (400 MHz, CDCl₃) 6.65 (s, 1H, NH), 4.77 (1H, dd, J = 9.7, 6.9, CHCHHO), 4.61 (1H, dd, J = 9.7, 2.1, CHCHHO), 3.89 (3H, s, OCH₃), 3.21 (1H, ddd, J = 6.9, 6.9, 2.1, CHCHCHHO), 2.95 (1H, dd, J = 17.4, 3.3, CHHCO₂^tBu), 2.81 (1H, ddd, J = 10.2, 6.9, 3.3, CHCHHCO₂^tBu), 2.47 (1H, dd, J = 17.4, 10.2, CHHCO₂^tBu), 1.44 (9H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 175.0 (C=O), 171.6 (C=O), 170.7 (C=O), 167.7 (C=O), 82.0 (OC(CH₃)₃), 72.3 (CHCH₂O), 66.4 (C), 54.1 (OCH₃), 46.9 (CHCHCH₂O), 44.0 (CHCH₂CO₂^tBu), 36.2 (CH₂CO₂^tBu), 28.2 (OC(CH₃)₃); ν_{max} 2980 (m, C-H), 1784 (s, C=O), 1720 (s, C=O),

1156 (m, C-O); HRMS (FI) found 313.1161, $[C_{14}H_{19}NO_7]$ requires 313.1175; $[\alpha]_D^{20} +15.0$ ($c = 1.00$, $CHCl_3$).

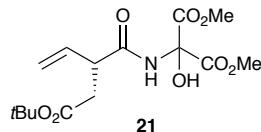


(R)-Dimethyl 2-acetoxy-2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)malonate 22



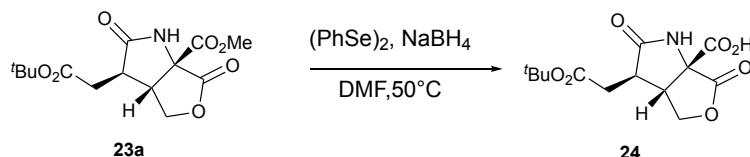
The title compound **22** was isolated as a by-product of the former cyclisation reaction (12.3 mg, no isolated yield given as most product was discarded with impure fractions). R_f 0.65 (1:3 EtOAc/PE); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, s, NH), 5.79–5.85 (1H, m, $CH=CHH'$), 5.33 (1H, d, $J = 16.9$, $CH=CHH'$), 5.27 (1H, d, $J = 9.9$, $CH=CHH'$), 3.82 (6H, s, OCH_3), 3.39–3.33 (1H, m, $CH(CO)N$), 2.77 (1H, dd, $J = 16.7, 7.6$, $CH'CO_2^tBu$), 2.45 (1H, dd, $J = 16.7, 6.1$, $CHH'CO_2^tBu$), 2.17 (3H, s, $O(CO)CH_3$), 1.42 (9H, s, $OC(CH_3)_3$); δ_c (100 MHz, $CDCl_3$) 171.6 ($C=O$), 170.4 ($C=O$), 170.0 ($C=O$), 164.0 ($C=O$), 163.9 ($C=O$), 134.2 ($CH=CH_2$), 119.7 ($CH=CH_2$), 81.6 (C_{quat}), 81.0 (C_{quat}), 54.2 (2 x OCH_3), 46.6 ($CH(CO)N$), 36.8 ($CH_2CO_2^tBu$), 28.0 ($OC(CH_3)_3$), 20.8 ($O(CO)CH_3$); ν_{max} 3341 (br, NH), 1767 (s, C=O), 1746 (m, C=O), 1728 (m, C=O), 1669 (m, C=O amide), 1243 (s, C-O), 1155 (m, C-O), 1059 (m); m/z (ESI $^+$) 410 ($[M+Na]^+$, 100%); HRMS found 410.1414, $C_{17}H_{25}NNaO_9$ requires 410.1422; $[\alpha]_D^{20} -38.2$ ($c = 1.00$, $CHCl_3$).

(R)-Dimethyl 2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido)-2-hydroxymalonate, 21



The title compound **22** was isolated as a by-product of the former cyclisation reaction (no isolated yield given as most product was discarded with impure fractions). R_f 0.40 (3:7 EtOAc/PE); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, s, NH), 5.86 (1H, ddd, $J = 16.2, 10.0, 7.0$, $CH=CHH'$), 5.32 (1H, d, $J = 16.2$, $CH=CHH'$), 5.27 (1H, d, $J = 10.0$, $CH=CHH'$), 5.05 (1H, s, OH), 3.85 (6H, s, OCH_3), 3.40 (1H, ddd, $J = 7.0, 7.0, 7.0$, $CH(CO)N$), 2.78 (1H, dd, $J = 16.5, 7.0$, $CHH'CO_2^tBu$), 2.44 (1H, dd, $J = 16.5, 7.0$, $CHH'CO_2^tBu$), 1.43 (9H, s, $OC(CH_3)_3$); δ_c (100 MHz, $CDCl_3$) 172.4 ($C=O$), 170.5 (2 x $C=O$), 167.2 ($C=O$), 134.5 ($CH=CH_2$), 119.5 ($CH=CH_2$), 81.1 ($OC(CH_3)_3$), 79.8 (NC-OH), 54.2 (2 x OCH_3), 46.8 ($CH(CO)N$), 36.8 ($CH_2CO_2^tBu$), 28.0 ($OC(CH_3)_3$); ν_{max} 3386 (br, O-H), 2680 (w, C-H), 1752 (s, C=O), 1728 (s, C=O), 1690 (s, C=O), 1293 (m), 1245 (m), 1154 (s, C-O); m/z (ESI $^+$) 368 ($[M+Na]^+$, 100%); HRMS found 368.1314 $C_{15}H_{23}NNaO_8$ requires 368.1316; $[\alpha]_D^{20} -46.8$ ($c = 0.5$ in $CHCl_3$).

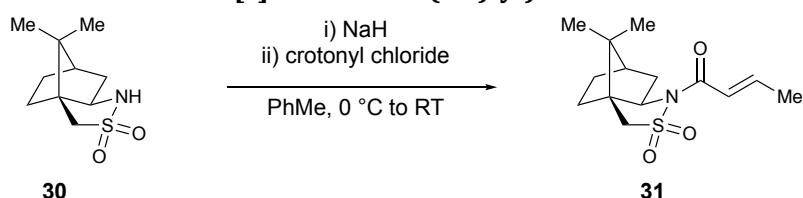
(3*R*,3*aR*,6*aR*)-3-(2-(tert-Butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a*-carboxylic acid 24



A solution of diphenyl diselenide (10.3 mg, 0.0328 mmol) in DMF (0.4 mL) at 100 °C under argon was treated with a solution of $NaBH_4$ (2.1 mg, 0.0547 mmol) in DMF (1 mL). The mixture was heated for 5

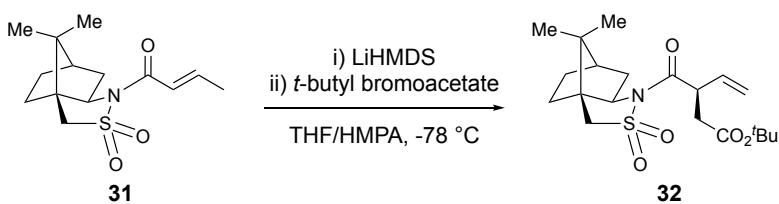
min at this temperature and cooled to 50 °C. A solution of lactone **23a** (17.1 mg, 0.0547 mmol) in DMF (0.2 mL) was then added. The reaction was stirred at 50 °C for 2 h. Water (5 mL) and a solution of pH 2 buffer (0.5 mL) were added at 22 °C and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried on Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:0 → 9:1 DCM:MeOH), which gave the carboxylic acid **24** (7.5 mg, 0.025 mmol, 46%). **m.p.** 150 °C (decomposed); δ_{H} (500 MHz, MeOD-*d*₄) 4.75 (dd, *J* = 9.1, 6.6, CHCHCH₂HO), 4.51 (1H, dd, *J* = 9.1, 1.3, CHCHCH₂HO), 3.18–3.12 (1H, m, CH), 2.85–2.79 (1H, m, CH), 2.82 (1H, dd, *J* = 17.7, 3.8, CHHCO₂^tBu), 2.52 (1H, dd, *J* = 17.7, 10.1, CHHCO₂^tBu), 1.48 (9H, s, OC(CH₃)₃); δ_{C} (126 MHz, MeOD-*d*₄) 178.6 (C=O), 177.3 (C=O), 172.5 (2 x C=O), 82.4 (C(CH₃)₃), 73.1 (CH₂HO), 49.3 (CH, under solvent peak), 45.6 (CH), 36.8 (CH₂CO₂^tBu), 28.4 (OC(CH₃)₃); ν_{max} 3257 (br, O-H), 2979 (w, C-H), 1772 (m, C=O), 1717 (s, C=O), 1656 (s, C=O), 1367 (s, m), 1157 (s, C-O); **m/z** (ESI⁺) 298 ([M-H]⁺, 100%); HRMS found 298.0933, [C₁₃H₁₆NO₇]⁺ requires 298.0932; $[\alpha]_{\text{D}}^{20}$ +31.4 (*c* = 0.50 in MeOH).

(E)-1-((3a*S*,6*R*,7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3*a*,6-methanobenzo[*c*]isothiazol-1(*4H*)-yl)but-2-en-1-one 30



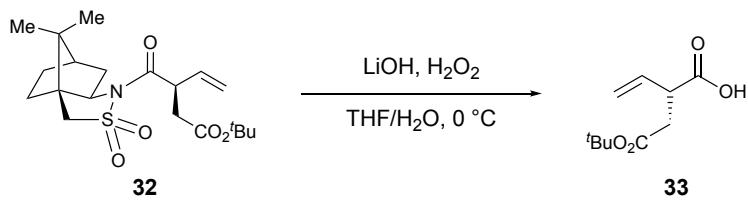
According to the modified procedure of Liang *et al.*⁴ NaH (60% dispersion in mineral oil, 3.36 g, 82.3 mmol) was added portionwise over 2 min to a vigorously stirred solution of (1*S*)-(–)-2,10-camphorsultam **30** (14.2 g, 65.9 mmol) in PhMe (350 mL) at 0 °C. The reaction was warmed to RT and stirred for 45 min. The mixture was then cooled to 0 °C and crotonyl chloride (7.9 mL, 82 mmol) was added over 15 min. The mixture was then warmed to RT and after 2 h stirring the reaction was quenched by slow addition of an aqueous solution HCl solution (1.0 M, 350 mL). The mixture was extracted with EtOAc (350 mL), and the organic layer was further washed with a saturated aqueous solution of NaHCO₃ (2 x 150 mL). The combined aqueous phases were treated with several portions of Na₂CO₃ until gas evolution ceased. This solution was further extracted with EtOAc (200 mL). The combined organic extracts were dried (Na₂SO₄), filtered and evaporated. The residue was recrystallised overnight at -20 °C from EtOAc/Hexane (1:5), which gave the title compound **31** as a white solid (14.1 g, 49.8 mmol, 76%). The mother liquor was concentrated under reduced pressure and was purified by flash column chromatography (PE:EtOAc 5:1) to give another batch of white solid (1.15 g, 4.06 mmol, 6%). R_f 0.79 (PE:EtOAc 3:7); **m.p.** (recrystallised batch) 176–180 °C, (lit. 180–183 °C); **δ**_H (500 MHz, CDCl₃) 7.09 (1H, dq, J = 14.5, 6.9, CH=CH-CH₃), 6.58 (1H, dd, J = 14.5, 1.3, CH=CH-CH₃), 3.93 (1H, dd, J = 7.6, 5.4, CHN), 3.51 (1H, d, J = 13.9, CHHSO₂), 3.44 (1H, d, J = 13.9, CHHSO₂), 2.17–2.10 (1H, m, CHHCHN), 2.08 (1H, dd, J = 13.9, 7.6, CHHCHN), 1.93 (3H, dd, J = 6.9, 1.3, CHCH₃), 1.91–1.84 (3H, m, CHC(CH₃)₂ and CHHCHHC and CHHCHHC), 1.46–1.31 (2H, m, CHHCHHC and CHHCHHC), 1.17 (3H, s, CH₃C), 0.97 (3H, s, CH₃C); **δ**_c (126 MHz, CDCl₃) 164.1 (C=O), 146.2 (CH=CH-CH₃), 122.4 (CH=CH-CH₃), 65.2 (C-N), 53.3 (CH₂SO₂), 48.6 (C), 47.9 (C), 44.8 (CHC(CH₃)₂), 38.6 (CH₂CHN), 33.0 (CH₂CH₂C), 26.6 (CH₂CH₂C), 20.9 (CH₃), 20.0 (CH₃), 18.5 (CHCH₃); **m/z** (ESI⁺) 284 ([M+H]⁺, 65%), 306 ([M+Na]⁺, 100%); [α]_D²⁰ = -98.4 (c = 1.00, CHCl₃, lit.⁴ +99.9, c = 1.00, CHCl₃, opposite enantiomer); **Data are consistent with literature values.**⁴

***tert*-butyl (R)-3-((3a*S*,6*R*,7*A*)-8,8-dimethyl-2,2-dioxidohexahydro-3*H*-3*a*,6-methanobenzo[*c*]isothiazole-1-carbonyl)pent-4-enoate 32**



According to the modified procedure of Oppolzer *et al.*,⁹ to a stirred mixture of LiHMDS in toluene (1.0 M, 72 mL, 72 mmol) and HMPA (25 mL) in THF (80 mL) at -78 °C was added dropwise a solution of α,β-unsaturated ketone **31** (13.5 g, 47.6 mmol) in THF (110 + 5 mL rinse) over 40 min. The mixture was stirred for 30 min and *t*-butyl bromoacetate (27.9 g, 143 mmol) was added dropwise over 30 min. After 7 h stirring at -78 °C, the reaction mixture was quenched by slow addition of pH 2 sulfate buffer (350 mL), and was then warmed to 22 °C. The mixture was extracted with EtOAc (600 mL). The organic layer was washed with water (500 mL) and brine (200 mL), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residual white solid was recrystallized from hexane, which gave ester **32** (17.5 g, 41.9 mmol, 88%) as a 95% pure^a white solid. A small amount of compound was purified by flash column chromatography (6:1 PE:EtOAc) for analytical purposes. **m.p.** 128–135 °C; **R_f** 0.53 (6:1 PE:EtOAc); δ_{H} (500 MHz, CDCl_3) 5.90 (1H, ddd, J = 17.5, 10.3, 7.8, $\text{CH}=\text{CH}_2$), 5.27 (1H, d, J = 17.5, $\text{CH}=\text{CHH}$), 5.21 (1H, d, J = 10.3, $\text{CH}=\text{CHH}$), 4.07 (1H, m, $\text{CHCH}=\text{CH}_2$), 3.90 (1H, dd, J = 7.9, 5.2, CHN), 3.51 (1H, d, J = 13.8, CHHSO_2), 3.43 (1H, d, J = 13.8, CHHSO_2), 2.86 (1H, dd, J = 15.0, 8.7, $\text{CHHCO}_2^t\text{Bu}$), 2.50 (1H, dd, J = 15.0, 5.2, $\text{CHHCO}_2^t\text{Bu}$), 2.22–2.14 (1H, m, CHHCHN), 2.04 (1H, dd, J = 13.9, 7.9 CHHCHN), 1.94–1.84 (3H, m, $\text{CHC}(\text{CH}_3)_2$ & CHHCH_2C & CH_2CHHC), 1.48–1.30 (11H, m, $\text{OC}(\text{CH}_3)_3$ & CHHCH_2C & CH_2CHHC), 1.23 (3H, s, CH_3), 0.98 (3H, s, CH_3); δ_c (100 MHz, CDCl_3) 172.0 ($\text{C}=\text{O}$), 170.1 ($\text{C}=\text{O}$), 133.8 ($\text{H}_2\text{C}=\text{CH}$), 118.5 ($\text{H}_2\text{C}=\text{CH}$), 81.0 ($\text{C}(\text{CH}_3)_3$), 65.5 (CHN), 53.2 (CH_2SO_2), 48.6 (C), 47.9 (C), 45.7 ($\text{CH}(\text{CO})$), 44.7 ($\text{CHC}(\text{CH}_3)_2$), 39.0 ($\text{CH}_2\text{CO}_2^t\text{Bu}$), 38.2 (CH_2CHN), 33.0 ($\text{CH}_2\text{CH}_2\text{CCH}_2\text{SO}_2$), 28.1 ($\text{OC}(\text{CH}_3)_3$), 26.6 ($\text{CH}_2\text{CH}_2\text{CCH}_2\text{SO}_2$), 20.7 (CH_3), 20.1 (CH_3); ν_{max} 2963 (w, C-H), 1729 (s, C=O), 1691 (s, C=O), 1331 (s, SO_2), 1216 (s, SO_2), 1154 (s); **m/z** (ESI⁺) 398 ($[\text{M}+\text{H}]^+$, 20%), 420 ($[\text{M}+\text{Na}]^+$, 100%); HRMS found 420.1802, $[\text{C}_{20}\text{H}_{31}\text{NNaO}_5\text{S}]^+$ requires 420.1815; $[\alpha]_D^{20}$ -63.0 (c = 1.00, CHCl_3).

(R)-2-(2-(tert-Butoxy)-2-oxoethyl)but-3-enoic acid

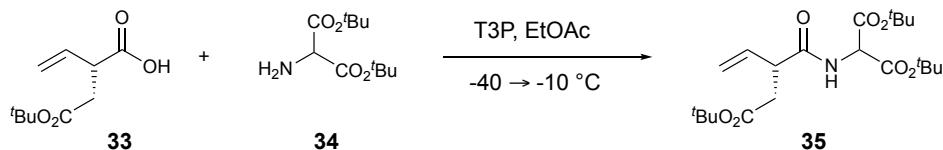


To a stirred solution of camphorsultam **32** (9.21 g, 22.0 mmol) in THF:H₂O (4:1, 165 mL) at 0 °C was added a solution of LiOH•H₂O (1.85 g, 44.0 mmol) and H₂O₂ (30%, 8.8 mL, 88 mmol) in H₂O (35 mL) over 3 min. The reaction mixture was stirred for 10 min and aq. Na₂S₂O₈ (2.4 M, 45 mL) was added over 3 min. The mixture was stirred at 0 °C for 3 min and then quenched by slow addition of pH 3 citric acid buffer (250 mL). The mixture was extracted with Et₂O (1×250 mL, 1×100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and, the solvent was removed *in vacuo*. The residue was triturated with hexane (30 mL). The precipitated chiral auxiliary was removed by filtration through cotton wool, and the solid was washed with more hexane (4×10 mL). The filtrate was concentrated *in*

^a Minor impurity is residual HMPA.

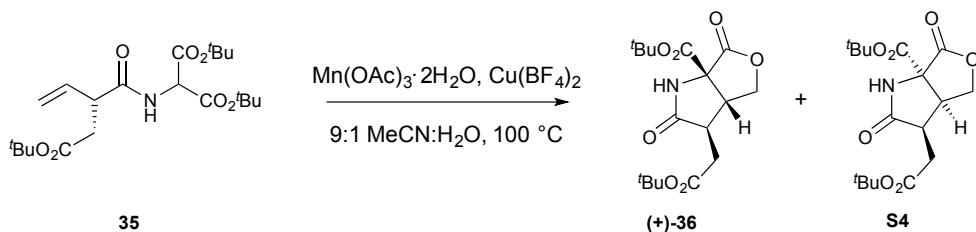
vacuo, which gave carboxylic acid **33** (4.56 g, 20.5 mmol, 91%) as a 90% pure^b colourless oil. A small amount of compound was purified by flash column chromatography (2→1:1 PE:EtOAc) for analytical purposes. R_f is not given as compound streaks in all solvent systems trialled; δ_H (400 MHz, CDCl₃) 5.87 (1H, ddd, *J* = 17.4, 10.2, 7.8, H₂C=CH), 5.24 (1H, d, *J* = 17.4 CH=CHH), 5.21 (1H, d, *J* = 10.2, CH=CHH), 3.50 (1H, m, CHCH=CH₂), 2.76 (1H, dd, *J* = 16.7, 8.7, CHHCO₂^tBu), 2.50 (1H, dd, *J* = 16.7, 5.7, CHHCO₂^tBu), 1.43 (9H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 178.6 (C=O), 170.5 (C=O), 133.8 (CH₂=CH), 118.5 (CH₂=CH), 81.4 (C), 45.6 (CHCH₂CO₂^tBu), 37.0 (CH₂CO₂^tBu), 28.1 (OC(CH₃)₃); ν_{max} 3500–2500 (br, OH), 2981 (w, C-H), 1731 (s, C=O), 1709 (s, C=O), 1369 (w), 1155 (s); m/z (ESI⁺) 199 ([M-H]⁺, 100%); HRMS found 199.0868, [C₁₀H₁₅O₄]⁺ requires 199.0976; $[\alpha]_D^{20}$ -32.5 (*c* = 1.00, CHCl₃).

(R)-Di-tert-butyl 2-(2-(tert-butoxy)-2-oxoethyl)but-3-enamido malonate 35



According to the modified procedure of Dunetz *et al.*,¹⁰ to a solution of (R)-2-(2-(tert-butoxy)-2-oxoethyl)but-3-enoic acid **33** (4.40 g, 22.0 mmol) in EtOAc (21 mL) at -10 °C were successively added pyridine (9 mL) and di-tert-butyl 2-aminomalonate **34** (6.10 g, 26.4 mmol). The vigorously stirred mixture was then cooled at -40 °C and propane phosphonic acid anhydride (T3P) (50% in EtOAc, 21 mL, 35 mmol) was added dropwise over 30 min. The reaction mixture was warmed up to -10 °C over 6 h (+5 °C every 60 min). The reaction was stirred at this temperature for 30 min and was quenched by addition of sat. aq. NH₄Cl (50 mL) and water (100 mL). The mixture was extracted with EtOAc (1×150 mL, 2×75 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (8→6:1 PE:EtOAc), which gave amidomalonate **35** (6.05 g, 14.4 mmol, 65% over 2 steps) as a colourless oil. R_f 0.49 (6:1 PE:EtOAc); δ_H (400 MHz, CDCl₃) 6.67 (1H, d, *J* = 6.7, NH), 5.89 (1H, ddd, *J* = 17.2, 10.2, 7.0, H₂C=CH), 5.33 (1H, dd, *J* = 17.2, 1.0, CH=CHH), 5.28 (1H, dd, *J* = 10.2, 1.0, CH=CHH), 4.89 (1H, d, *J* = 6.7, NCH), 3.42 (1H, ddd, *J* = 7.0, 7.0, 7.0, CH(CO)_N), 2.83 (1H, dd, *J* = 16.3, 7.0, CHHCO₂^tBu), 2.45 (1H, dd, *J* = 16.3, 7.0, CHHCO₂^tBu), 1.49 (9H, s, OC(CH₃)₃), 1.48 (9H, s, OC(CH₃)₃), 1.43 (9H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 171.5 (C=O), 170.9 (C=O), 165.5 (C=O), 165.4 (C=O), 135.3 (H₂C=CH), 119.3 (H₂C=CH), 83.3 (OC(CH₃)₃), 83.3 (OC(CH₃)₃), 80.9 (OC(CH₃)₃), 58.0 (NCH), 47.1 (CH(CO)_N), 37.1 (CH₂CO₂^tBu), 28.2 (OC(CH₃)₃), 27.9 (2 × OC(CH₃)₃); ν_{max} 2980 (w, C-H), 1752 (m, C=O), 1733 (s, C=O), 1684 (m, C=O), 1394 (m), 1251 (m), 1149 (s, C-O), 845 (w); m/z (ESI⁺) 436 ([M+Na]⁺, 100%); HRMS found 436.2297, [C₂₁H₃₅NNaO₇]⁺ requires 436.2303; $[\alpha]_D^{20}$ = -38.5 (*c* = 1.00, CHCl₃).

(3*R*,3*aR*,6*aS*)-tert-Butyl 3-(2-(tert-butoxy)-2-oxoethyl)-2,6-dioxohexahydro-1*H*-furo[3,4-b]pyrrole-6*a*-carboxylate (+)-36



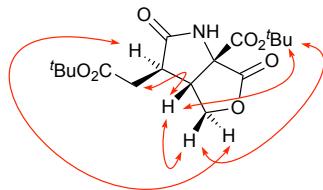
This first procedure was applied when the positive influence of water was discovered. The final optimised conditions are given at the end of this page. In an oil bath at 100 °C, a boiling solution of amidomalonate **35** (5.93 g, 14.4 mmol) in N₂ sparged MeCN:H₂O (9:1, 53 mL) under Ar was treated by

^b Minor impurity is residual chiral auxiliary.

simultaneous and quick addition of $\text{Mn}(\text{OAc})_3 \bullet 2\text{H}_2\text{O}$ (11.5 g, 43.1 mmol) and $\text{Cu}(\text{BF}_4)_2 \bullet 6\text{H}_2\text{O}$ (1.49 g, 4.31 mmol). The reaction mixture was stirred vigorously for 40 min at 100 °C and was then cooled to 22 °C. The brown suspension was plugged through a one inch silica pad (rinsing with 3 x 10 mL of $\text{H}_2\text{O}/\text{EtOAc}$ 1:1, all rinsing liquids were loaded on the pad). The pad was eluted with EtOAc, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (2:1 Et₂O:pentane), which gave the title compound (+)-**36** as a white solid (3.42 g, 9.62 mmol, 67%) along with the minor diastereomer **S4** (0.34 g, 0.95 mmol, 7%) contaminated with the *exo*-alkene **37**.

Data for the major diastereomer (+)-**36**:

m.p. 147–151 °C; **R_f** 0.40 (2:1 Et₂O:PE_{30–40} 2:1); **δ_H** (400 MHz, CDCl₃) 6.68 (1H, s, NH), 4.69 (1H, dd, *J* = 9.6, 7.0, CHCHHO), 4.58 (1H, dd, *J* = 9.6, 1.7, CHCHHO), 3.12 (1H, ddd, *J* = 7.0, 7.0, 1.7, CHCH₂O), 2.94 (1H, dd, *J* = 17.2, 3.2, CHHCO₂^tBu), 2.78 (1H, ddd, *J* = 10.4, 7.0, 3.2, CHCH₂CO₂^tBu), 2.47 (1H, dd, *J* = 17.2, 10.4, CHHCO₂^tBu), 1.51 (9H, s, OC(CH₃)₃), 1.41 (9H, s, OC(CH₃)₃); **δ_C** (100 MHz, CDCl₃) 175.1 (C=O), 172.1 (C=O), 170.8 (C=O), 166.0 (C=O), 85.6 (C), 81.9 (C), 72.1 (CH₂O), 66.9 (C), 47.1 (CHCH₂O), 44.0 (CHCH₂CO₂^tBu), 36.2 (CH₂CO₂^tBu), 28.2 (C(CH₃)₃), 27.9 (C(CH₃)₃); **v_{max}** 2980 (w, C-H), 1782 (m, C=O), 1717 (s, C=O), 1151 (s, C-O); **m/z** (ESI⁺) 378 ([M+Na]⁺, 100%); HRMS found 378.1512, [C₁₇H₂₅NNaO₇]⁺ requires 378.1523; $[\alpha]_D^{20}$ +17.8 (*c* = 1.00, CHCl₃).

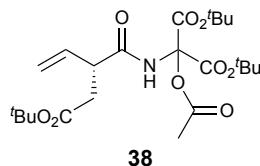


Data for the minor diastereomer **S4**:

R_f 0.44 (1:1 PE:Et₂O); **δ_H** (400 MHz, CDCl₃) 7.06 (1H, br, NH), 4.55 (1H, dd, *J* = 9.8, 8.7, OCHH), 4.17 (1H, dd, *J* = 9.8, 6.3, OCHH), 3.70 (1H, ddd, *J* = 15.0, 8.7, 6.3, OCH₂CH), 3.10 (1H, m, CHCH₂CO₂^tBu), 2.90 (1H, dd, *J* = 17.4, 3.9, CHHCO₂^tBu), 2.34 (1H, dd, *J* = 17.4, 11.7, CHHCO₂^tBu), 1.50 (9H, s, OC(CH₃)₃), 1.44 (9H, s, OC(CH₃)₃); **δ_C** (100 MHz, CDCl₃) 175.5 (C=O), 171.3 (C=O), 170.8 (C=O), 166.4 (C=O), 85.3 (OC(CH₃)₃), 82.0 (OC(CH₃)₃), 67.5 (OCH₂), 67.0 (C), 42.7 (CHCH₂CO₂^tBu), 39.8 (OCH₂CH), 32.3 (CH₂CO₂^tBu), 28.1 (OC(CH₃)₃), 27.9 (OC(CH₃)₃); **v_{max}** 2980 (w, C-H), 1784 (m, C=O), 1714 (s, C=O), 1244 (m, C=O), 1148 (s, C=O), 731 (m); **m/z** (ESI⁺) 378 ([M+Na]⁺, 100%); HRMS found 378.1512, [C₁₇H₂₅NNaO₇]⁺ requires 378.1523; $[\alpha]_D^{20}$ -64.1 (*c* = 1.00 in CHCl₃).

After full optimisation of the H₂O/MeCN ratio, the reaction was performed according to the same procedure on malonate **35** of 82% ee (4.06 g, 0.82 mmol) using $\text{Mn}(\text{OAc})_3 \bullet 2\text{H}_2\text{O}$ (7.89 g, 29.5 mmol) and $\text{Cu}(\text{BF}_4)_2 \bullet 6\text{H}_2\text{O}$ (1.01 g, 0.295 mmol) in MeCN/H₂O (50:3, 37 mL) which gave the major diastereomer (+)-**36** (2.48 g, 6.97 mmol, 71%) and the minor diastereomer **36** (325 mg, 0.914 mmol, 9%).

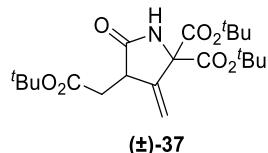
Di-*tert*-butyl (*R*)-2-acetoxy-2-(2-(*tert*-butoxy)-2-oxoethyl)but-3-enamido malonate **38**



The compound **38** was isolated as a side product of the manganese(III) and copper(II)-mediated cyclisation of **35**, when the reaction was carried without water – the compound was characterised on optically active material. **R_f** 0.58 (1:2 PE:Et₂O); **δ_H** (400 MHz, CDCl₃) 7.62 (1H, br, NH), 5.81 (1H, ddd, *J* = 17.1, 10.0, 8.3, CH=CHH), 5.30 (1H, d, *J* = 17.1, CH=CHH), 5.26 (1H, d, *J* = 10.0, CH=CHH), 3.35 (1H, dd, *J* = 7.0, 7.0, CHCHHCO₂^tBu), 2.79 (1H, dd, *J* = 16.6, 7.0, CHHCO₂^tBu), 2.41 (1H, dd, *J* = 16.6, 7.0,

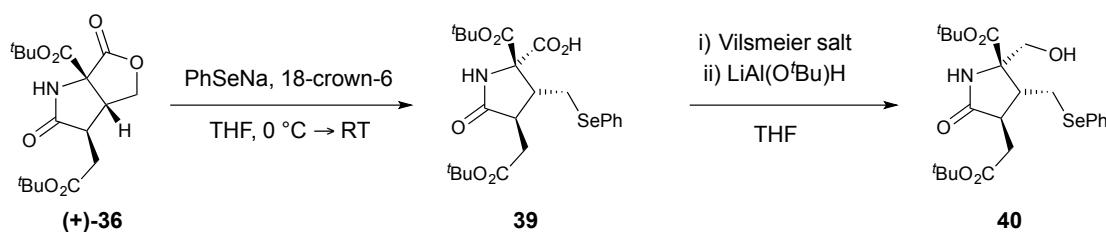
$\text{CHHCO}_2^t\text{Bu}$), 2.14 (3H, s, $(\text{CO})\text{CH}_3$), 1.46 (9H, s, $\text{OC}(\text{CH}_3)_3$), 1.45 (9H, s, $\text{OC}(\text{CH}_3)_3$), 1.41 (9H, s, $\text{OC}(\text{CH}_3)_3$); δ_c (100 MHz, CDCl_3) 170.9 (C=O), 170.6 (C=O), 169.9 (C=O), 162.3 (C=O), 162.0 (C=O), 134.7 (CH=CH_2), 119.4 (CH=CH_2), 84.4 (C), 84.2 (C), 82.0 (C), 80.9 (C), 46.9 ($\text{CHCH}_2\text{CO}_2^t\text{Bu}$), 36.9 ($\text{CH}_2\text{CO}_2^t\text{Bu}$), 28.2 ($\text{OC}(\text{CH}_3)_3$), 27.8 ($\text{OC}(\text{CH}_3)_3$), 27.7 ($\text{OC}(\text{CH}_3)_3$), 20.9 ($(\text{CO})\text{CH}_3$); ν_{max} 2979 (w, C-H), 1758 (s, C=O), 1699 (m, C=O), 1248 (m), 1150 (s), 1058 (w), 842 (s); m/z (ESI $^+$) 494.3 ($[\text{M}+\text{Na}]^+$, 100%); HRMS found 494.2359, $[\text{C}_{23}\text{H}_{37}\text{NNaO}_9]^+$ requires 494.2361; $[\alpha]_D^{20}$ -32.2 ($c = 1.00$ in CHCl_3).

Di-*tert*-butyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate (\pm)-37



The compound (\pm)-37 (impure) was isolated as a side product of the manganese(III) and copper(II)-mediated cyclisation of (\pm)-35 as a colourless oil, when the reaction was carried with an excess of water. R_f 0.46 (1:2 PE:Et₂O); *pure material could not be obtained and hence unambiguous proton and carbon NMR assignments of resonances was not always possible*; NMR δ_H (400 MHz, CDCl₃) 6.37 (1H, s, NH), 5.75 (1H, d, J = 2.6, =CHH), 5.40 (1H, d, J = 2.6, =CHH), 3.39 (1H, ddd, J = 7.1, 4.7, 2.6, CHCHHCO₂^tBu), 2.72 (1H, dd, J = 16.4, 4.7, CHHCO₂^tBu), 2.42 (1H, dd, J = 16.4, 7.1, CHHCO₂^tBu), 1.51–1.41 (27H, 3 x s, 3 x OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 175.5 (C=O), 170.1 (C=O), 166.3 (C=O), 165.7 (C=O), 140.6 (C=CH₂), 114.6 (C=CH₂), 83.8 (C), 83.8 (C), 81.3 (C), 71.8 (C), 41.8 (CH), 36.3 (CH), 28.1 (2 x OC(CH₃)₃), 27.9 (OC(CH₃)₃); ν_{max} 2978 (w, C-H), 1714 (s, C=O), 1250 (m), 1145 (s), 845 (s); **m/z** (ESI⁺) 434.3 ([M+Na]⁺, 100%); HRMS found 434.2140, [C₂₁H₃₃NNaO₇]⁺ requires 434.2149.

(2S,3R,4R)-4-(2-(tert-butoxy)-2-oxoethyl)-2-(tert-butoxycarbonyl)-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylic acid 39 and tert-butyl (2S,3R,4R)-4-(2-(tert-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate 40

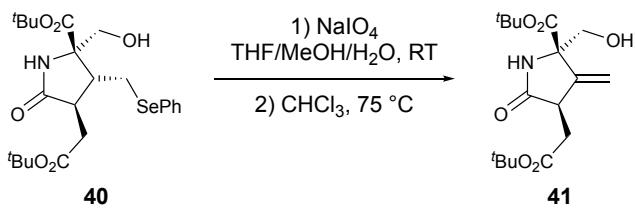


According to the modified procedure of Eustache *et al.*,¹¹ to a degassed solution of diphenyl diselenide (3.16 g, 10.1 mmol) in THF (16 mL) under Ar at 22 °C was added NaH (60% dispersion in oil, 811 mg, 20.2 mmol). The mixture was stirred vigorously for 90 min at 65 °C and was then cooled to 0 °C. A solution of lactone **36** (3.00 g, 8.45 mmol) and 18-crown-6 (558 mg, 2.11 mmol) in THF (25 + 3 mL rinse) was added over 1 min. The reaction mixture was stirred for 3 h at 22 °C and then quenched by successive addition of MeOH (5 mL) and H₂O (5 mL). Air was bubbled through this mixture for 45 min, and then DCM (150 mL) was added and the mixture was extracted with aqueous NaOH (0.10 M, 1×150 mL and 2×75 mL). The combined aqueous extracts were carefully acidified at 0 °C with pH 2 sulfate buffer (200 mL). The aqueous was extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na₂SO₄), filtered and the solvent was removed *in vacuo*, which gave the crude carboxylic acid **39** (4.87 g) as a white solid which was used without purification. **m.p.** 152–158 °C; **R**_f 0.73 (40:5:1 EtOAc:MeOH:AcOH); **δ**_H (400 MHz, methanol-*d*₄) 7.56 (2H, dd, *J* = 8.0, 1.3, ArH), 7.31–7.17 (3H, m,

ArH), 3.72 (1H, dd, *J* = 12.3, 2.1, *CHHSe*), 3.10–2.98 (1H, m, *CHCH₂Se*), 2.95–2.83 (2H, m, *CHHSe* and *CHHCO₂tBu*), 2.76 (1H, dd, *J* = 17.2, 4.6, *CHHCO₂tBu*), 2.73–2.66 (1H, m, *CHCH₂CO₂tBu*), 1.46 (9H, s, OC(CH₃)₃), 1.33 (9H, s, OC(CH₃)₃); δ_c (100 MHz, methanol-*d*₄) 179.7 (*C=O*), 172.2 (2 x *C=O*), 171.4 (*C=O*), 133.1 (*Ar*), 131.2 (*Ar*), 130.2 (*Ar*), 127.8 (*Ar*), 83.0 (*C(CH₃)₃*), 82.0 (*C(CH₃)₃*), 74.6 (*C*), 46.2 (*CHCH₂CO₂tBu*), 44.2 (*CHCH₂Se*), 36.6 (*CH₂CO₂tBu*), 29.7 (*CH₂Se*), 28.3 (*C(CH₃)₃*), 28.2 (*C(CH₃)₃*); ν_{max} 3283 (br, O-H), 2979 (w, C-H), 1723 (s, *C=O*), 1695 (s, *C=O*), 1618 (s, *C=O*), 1368 (m), 1155 (s), 735 (w); HRMS (FI and ESI⁺) showed no detectable ionisation; $[\alpha]_D^{20}$ +1.6 (*c* = 1.00, MeOH).

To a solution of DMF (1.31 mL, 16.9 mmol) in dry DCM (65 mL) at 0 °C was added oxalyl chloride (4.6 mL, 51 mmol) over 5 min (*caution! gas evolution*). The reaction was stirred for 30 min at 22 °C and all volatiles were removed under reduced pressure. The residual white Vilsmeier salt was dried under high vacuum for a further 20 min before being redissolved in THF (65 mL) and MeCN (45 mL). A solution of crude carboxylic acid **39** (4.87 g) in THF (40 + 10 mL rinse) was then added over 10 min at 0 °C. The reaction was stirred at 0 °C for 30 min and cooled to –78 °C. LiAl(O^tBu)₃H (17.2 g, 67.6 mmol) in THF (115 mL) was added dropwise *via* cannula over 15 min. The reaction mixture was stirred for 10 min at –78 °C and then allowed to warm to 22 °C. After 90 min, the reaction was quenched by careful addition of sat. aq. NH₄Cl (75 mL), water (75 mL) and sat. aq. Rochelle’s salt (300 mL). After 3 h stirring, the mixture was extracted with EtOAc (1×200 mL, 2×100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (EtOAc), which gave alcohol **40** (3.40 g, 6.82 mmol, 81% over 2 steps) as a colourless solid. **m.p.** 30–35 °C; **R**_f 0.66 (EtOAc); δ _H (500 MHz, CDCl₃) 7.54–7.50 (2H, m, ArH), 7.28–7.22 (3H, m, ArH), 7.11 (1H, s, NH), 3.90 (1H, m, OH) 3.89 (1H, dd, *J* = 17.6, 7.6, CHHOH), 3.81 (1H, m, CHHOH), 3.52 (1H, dd, *J* = 12.3, 4.3, CHHSe), 3.14 (1H, dd, *J* = 12.3, 10.2, CHHSe), 2.89 (1H, dd, *J* = 16.2, 4.1, CHHCO₂^tBu), 2.80 (1H, m, CHCH₂CO₂^tBu), 2.76 (1H, dd, 16.2, 5.0, CHHCO₂^tBu), 2.67 (1H, td, *J* = 10.2, 4.3, CHCH₂Se), 1.35 (9H, s, C(CH₃)₃) ; δ _C (126 MHz, CDCl₃) 177.8 (C=O), 170.9 (C=O), 170.6 (C=O), 133.0 (Ar), 129.7 (Ar), 129.3 (Ar), 127.3 (Ar), 83.0 (C(CH₃)₃), 81.0 (C(CH₃)₃), 68.4 (C), 64.2 (CH₂OH), 45.4 (CH), 45.2 (CH), 36.1 (CH₂CO₂^tBu), 28.2 (C(CH₃)₃), 27.9 (C(CH₃)₃), 27.2 (CH₂Se); ν _{max} 3356 (br, O-H), 2979 (w, C-H), 1767 (m, C=O), 1724 (s, C=O), 1700 (s, C=O), 1369 (w), 1154 (s), 739 (w); **m/z** (ESI⁺) 522.1 ([M+Na]⁺, 100%); HRMS found 522.1358, [C₂₃H₃₃NNaO₆Se]⁺ requires 522.1367; $[\alpha]_D^{20}$ -59.2 (c = 1.00, CHCl₃).

(2S,4R)-tert-Butyl 4-(2-(tert-butoxy)-2-oxoethyl)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylate 41

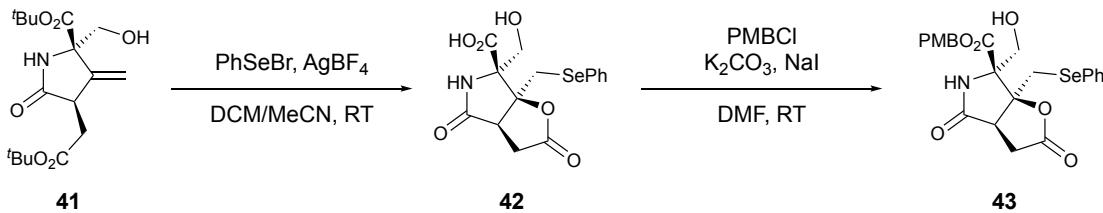


According to the modified procedure of Kocienski *et al.*,⁵ to a mixture of lactam **40** (3.40 g, 6.23 mmol) and NaHCO₃ (2.62 g, 31.2 mmol) in 1:1:1 MeOH/H₂O/THF (135 mL) at 22 °C was added NaIO₄ (7.92 g, 31.2 mmol) portionwise over 3 min. The reaction mixture was stirred under air for 45 min. The reaction was then diluted with H₂O (150 mL) and CHCl₃ (150 mL) and stirring was continued for 5 min. The mixture was filtered through Celite™, eluting with CHCl₃ (2×35 mL). The layers were separated and the aqueous phase was extracted with CHCl₃ (2×70 mL). The combined organic extracts were dried (Na₂SO₄), filtered, sparged with argon (5 min) and heated under reflux at 75 °C for 60 min. The mixture was cooled to 22 °C, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:PE, then 50:1 EtOAc:MeOH) which gave alkene **41** (2.13 g, 6.23 mmol, 100%) as a white solid. R_f 0.60 (EtOAc); **m.p.** 158–167 °C; δ _H (400 MHz, CDCl₃) 6.51 (1H, br, NH), 5.46 (1H, dd, *J* = 3.0, 0.5, C=CHH), 5.24 (1H, dd, *J* = 2.3, 0.5, C=CHH), 4.09 (1H, d, *J* = 11.1, CHHOH), 3.64 (1H,

$d, J = 11.1$, CHHOH), 3.41 (1H, m, $CHCH_2CO_2^tBu$), 2.82 (1H, dd, $J = 16.7, 4.6$, $CHHCO_2^tBu$), 2.57 (1H, dd, $J = 16.7, 8.1$, $CHHCO_2^tBu$), 1.49 (9H, s, $C(CH_3)_3$), 1.43 (9H, s, $C(CH_3)_3$); δ_c (100 MHz, $CDCl_3$) 176.9 ($C=O$), 170.4 ($C=O$), 169.5 ($C=O$), 144.1 ($CH_2=C$), 111.3 ($CH_2=C$), 83.1 ($C(CH_3)_3$), 81.3 ($C(CH_3)_3$), 71.0 (C), 68.7 (CH_2OH), 42.6 (CH), 36.8 ($CH_2CO_2^tBu$), 28.1 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$); ν_{max} 3339 (br, O-H), 2978 (w, C-H), 1725 (s, $C=O$), 1710s (s, $C=O$), 1660 (m, $C=O$), 1368 (m), 1152(s), 845 (w); m/z (ESI $^+$) 364 ($[M+Na]^+$, 100%); HRMS found 364.1727, $[C_{17}H_{27}NNaO_6]^+$ requires 364.1731; $[\alpha]_D^{20}$ -32.5 ($c = 1.00$, $CHCl_3$).

(3aR,6R,6aS)-6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2H-furo[2,3-c]pyrrole-6-carboxylic acid 42 and

(3aR,6R,6aS)-4-Methoxybenzyl 6-(hydroxymethyl)-2,4-dioxo-6a-((phenylselanyl)methyl)hexahydro-2H-furo[2,3-c]pyrrole-6-carboxylate 43

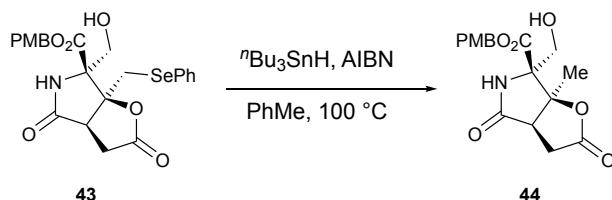


According to the modified procedure of Danishefsky *et al.*,¹² to a vigorously stirred solution of alkene **41** (2.13 g, 6.23 mmol) in degassed DCM:MeCN (1:1, 115 mL) under argon were successively and quickly added PhSeBr (5.15 g, 21.8 mmol) and $AgBF_4$ (3.03 g, 15.6 mmol). The reaction mixture was stirred at 22 °C for 7 h. The reaction was diluted with Et_2O (200 mL) and pH 2 sulfate buffer (200 mL) and the aqueous phase was saturated with NaCl and further extracted with EtOAc (8×70 mL). The combined organic layers were extracted with aq. NaOH (0.50 M, 1×100 mL, 1×50 mL). The combined aqueous extracts were treated at 0 °C with pH 2 sulfate buffer (75 mL) followed by dropwise addition of conc. aq. HCl until the pH reached 2. The cloudy suspension was extracted with EtOAc (1×150 mL, 8×70 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*, which gave carboxylic acid **42** (2.41 g), which was used without purification. R_f 0.53 (EtOAc:MeOH 4:1 + 2.5% AcOH); δ_H (400 MHz, $DMSO-d_6$) 7.59–7.52 (2H, m, ArH), 7.33–7.21 (3H, m, ArH), 4.10 (1H, d, $J = 13.7$, $CHHSe$), 3.97 (1H, d, $J = 11.5$, CHHOH), 3.83 (1H, d, $J = 13.7$ Hz, $CHHSe$), 3.44 (1H, m, CHHOH), 2.93 (1H, dd, $J = 17.9, 9.9$, O(CO)CHH), 2.77 (1H, d, $J = 9.9$, N(CO)CH), 2.42 (1H, d, $J = 17.9$, O(CO)CHH); δ_c (126 MHz, $DMSO-d_6$) 174.7 ($C=O$), 173.2 ($C=O$), 170.3 ($C=O$), 130.8 (Ar), 130.6 (Ar), 129.3 (Ar), 126.8 (Ar), 91.8 (C), 73.5 (C), 64.5 (CH_2OH), 47.8 (N(CO)CH), 33.3 (O(CO)CH₂), 31.6 (CH_2Se); ν_{max} 3293 (br, O-H), 1781 (m, $C=O$), 1701 (s, $C=O$), 1160 (m), 739(w); m/z (ESI $^+$) 384 ($[M-H]^-$, 100%); HRMS found 383.9985, $[C_{15}H_{14}NNO_6Se]^-$ requires 383.9993.

A solution of crude carboxylic acid **42** (2.39 g, 6.23 mmol), K_2CO_3 (3.45 g, 24.7 mmol), PMBCl (2.97 g, 18.9 mmol), and NaI (3.45 g, 18.9 mmol) in DMF (20 mL) was heated at 40 °C for 4 h. The reaction mixture was cooled to 22 °C, diluted with EtOAc (150 mL) and successively washed with water (3×100 mL) and brine (100 mL). The combined organic extracts was dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (100:20:1 EtOAc:PE:MeOH), which gave lactone **43** (2.31 g, 5.26 mmol, 84% over 2 steps) as a white solid. **m.p.** 67–71 °C; R_f 0.33 (EtOAc); δ_H (400 MHz, $CDCl_3$) 7.73 (1H, s, NH), 7.50–7.47 (2H, m, ArH), 7.26–7.23 (3H, m, ArH), 7.20 (2H, d, $J = 8.2$, ArH), 6.85 (2H, d, $J = 8.2$, ArH), 5.12 (1H, d, $J = 11.9$, $CHHAr$), 5.04 (1H, d, $J = 11.9$, $CHHAr$), 4.00 (1H, d, $J = 11.7$, CHHOH), 3.79 (3H, s, OCH_3), 3.70 (1H, d, $J = 11.7$, CHHOH), 3.69 (s, 2H, CH_2Se), 3.13 (1H, dd, $J = 18.1, 10.0$, O(CO)CHH), 2.94 (1H, d, $J = 10.0$, N(CO)CH), 2.69 (1H, d, $J = 18.1$, O(CO)CHH); δ_c (100 MHz, $CDCl_3$) 173.5 ($C=O$), 167.5 ($C=O$), 160.1 ($C=O$), 132.2 (Ar), 130.4 (Ar) 129.7 (Ar), 129.5 (Ar), 127.9 (Ar), 126.6 (Ar), 114.2 (Ar), 90.7 (C), 74.3 (C), 68.5 (CH_2OH), 64.0 (CH_2Ar), 55.4 (OCH_3), 48.0 (CH), 33.4 (CH_2 lactone), 31.8 (CH_2Se); ν_{max} 3316 (br, OH), 1788 (m, $C=O$),

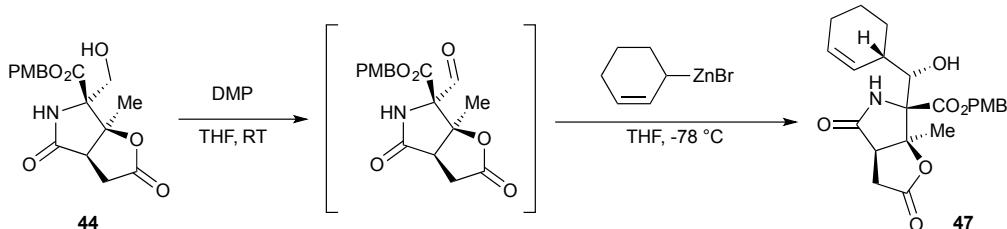
1730 (m, C=O), 1709 (s, C=O), 1245 (s), 734 (m); **m/z** (ESI⁺) 528 ([M+Na]⁺, 100%); HRMS found 528.0529, [C₁₉H₂₃NNaO₆Se]⁺ requires 528.0532; [α]_D²⁰ +10.9 (c = 1.00, CHCl₃).

(3aR,6R,6aS)-4-Methoxybenzyl 6-(hydroxymethyl)-6a-methyl-2,4-dioxohexahydro-2H-furo[2,3-c]pyrrole-6-carboxylate 44



According to the modified procedure of Danishefsky *et al.*,^[8] to a solution of AIBN (49.0 mg, 0.297 mmol) and lactone **43** (1.50 g, 2.97 mmol) was added *n*Bu₃SnH (2.0 mL, 7.4 mmol). The reaction flask was plunged into a pre-heated oil bath (100 °C) and stirred at this temperature for 45 min. The reaction mixture was cooled to 22 °C and passed through a silica pad (1:1 EtOAc:PE, 3 CV then 20:1 EtOAc:MeOH, 10 CV), which gave alcohol **44** (963 mg, 2.76 mmol, 93%) as a white solid. **m.p.** 184–191 °C; **R**_f 0.53 (EtOAc:MeOH 20:1); **δ**_H (500 MHz, DMSO-d₆) 8.54 (1H, s, NH), 7.33 (2H, d, *J* = 8.7, ArH), 6.93 (2H, d, *J* = 8.7, ArH), 5.50 (1H, dd, *J* = 5.0, 5.0, CH₂OH), 5.14 (1H, d, *J* = 12.2, CHHAr), 5.09 (1H, d, *J* = 12.2, CHHAr), 3.78 (1H, dd, *J* = 10.9, 5.0, CHHOH), 3.75 (3H, s, OCH₃), 3.61 (1H, dd, *J* = 10.9, 5.0, CHHOH), 3.07 (1H, dd, *J* = 17.8, 9.5, CHH(CO)O), 2.96 (1H, d, *J* = 9.5, N(CO)CH), 2.49 (1H, d, *J* = 17.8, CHH(CO)O), 1.58 (3H, s, CCH₃); **δ**_C (126 MHz, DMSO-d₆) 173.7 (C=O), 173.6 (C=O), 168.1 (C=O), 159.2 (Ar), 129.6 (Ar), 127.4 (Ar), 113.8 (Ar), 89.8 (C), 72.3 (C), 66.5 (CH₂Ar), 63.3 (CH₂OH), 55.1 (OCH₃), 47.4 (CH), 30.3 (CH₂ lactone), 18.6 (CCH₃); **v**_{max} 3329 (br, OH), 1785 (m, C=O), 1741 (m, C=O), 1709 (m, C=O), 1516 (w), 1246 (m); **m/z** (ESI⁺) 372 ([M+Na]⁺, 100%); HRMS found 372.1057, [C₁₇H₁₉NNaO₇]⁺ requires 372.1054; [α]_D²⁰ +72.1 (c = 1.00, MeOH).

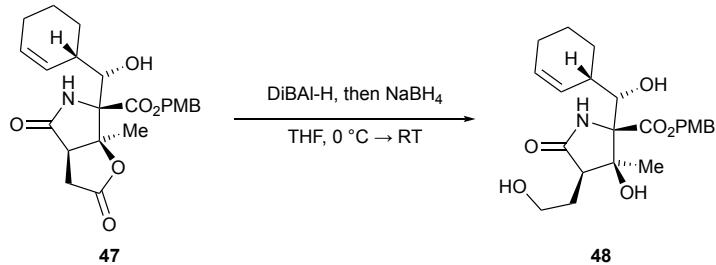
(3aR,6R,6aS)-4-Methoxybenzyl 6-((S)-((S)-cyclohex-2-en-1-yl)(hydroxymethyl)-6a-methyl-2,4-dioxohexahydro-2H-furo[2,3-c]pyrrole-6-carboxylate 47



To a vigorously stirred suspension of zinc dust (2.11 g, 32.2 mmol) in degassed THF (39 mL) under Ar at 0 °C was added 3-bromocyclohexene (3.1 mL, 26.9 mmol) dropwise over 5 min. This mixture was stirred for 90 min. In the meantime, degassed THF (28 mL) was added to DMP (2.28 g) and alcohol **44** (938 mg, 2.69 mmol) at 22 °C. The mixture was stirred for 75 min and was added to the cyclohex-2-en-1-ylzinc(II) bromide solution at -78 °C over 10 min. The reaction mixture was stirred for 10 min at -78 °C and was quenched by addition of sat. aq. NH₄Cl solution (40 mL) and water (10 mL). The stirred mixture was warmed to 22 °C and extracted with EtOAc (3×40 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (4:1 EtOAc:PE), which gave alcohol **47** (645 mg, 1.50 mmol, 56% over 2 steps) as a white solid. **m.p.** 79–85 °C; **R**_f 0.54 (EtOAc); **δ**_H (500 MHz, CDCl₃) 7.34–7.29 (2H, m, ArH), 6.94 (1H, br, NH), 6.90–6.86 (2H, m, ArH), 6.00 (1H, ddd, *J* = 10.0, 5.1, 3.6, CH=CH), 5.57 (1H, dd, *J* = 10.0, 2.0, CH=CH), 5.26 (1H, d, 11.8, CHHAr), 5.11 (1H, d, 11.8, CHHAr), 3.99 (1H, br s, CHOH), 3.80 (3H, s, OCH₃), 3.07 (1H, d, *J* = 9.3, N(CO)CH), 2.89 (1H, d, *J* = 18.3, CHH(CO)O), 2.75 (1H, dd, *J* = 18.3, 9.3,

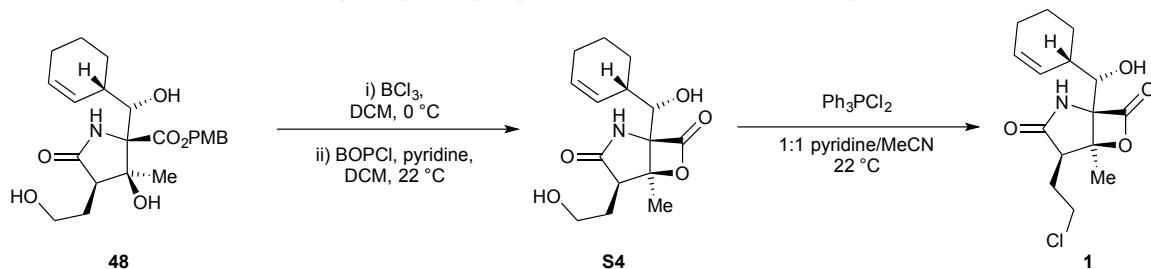
$\text{CHH}(\text{CO})\text{O}$, 2.44–2.24 (1H, br, OH), 2.08–2.01 (1H, m, CHCHOH), 2.00–1.85 (2H, m, CH_2 cyclohexene), 1.76 (3H, s, CCH_3), 1.68–1.59 (1H, m, CHH cyclohexene), 1.50–1.28 (m, 3H, CHH cyclohexene and CH_2 cyclohexene); δ_c (126 MHz, CDCl_3) 175.3 (C=O), 173.0 (C=O), 168.0 (C=O), 160.2 (Ar), 135.2 (CH alkene), 130.9 (Ar), 126.8 (Ar), 123.4 (CH alkene), 114.2 (Ar), 91.9 (C), 75.7 (CHOH), 75.5 (C), 68.1 (CH_2Ar), 55.4 (OCH_3), 48.3 (NC(O)CH), 37.5 (CHCHOH), 30.5 (CH_2 lactone), 28.3 (CH_2 cyclohexene), 24.9 (CH_2 cyclohexene), 20.5 (CH_2 cyclohexene), 19.7 (CH_3); ν_{max} 3310 (br, O-H), 2929 (w, C-H), 1786 (m, C=O), 1709 (s, C=O), 1246 (s), 731 (w); m/z (ESI $^+$) 452 ($[\text{M}+\text{Na}]^+$, 100%); HRMS found 452.1672, $[\text{C}_{23}\text{H}_{27}\text{NNaO}_7]^+$ requires 452.1680; $[\alpha]_D^{20}$ -22.9 (c = 1.00, CHCl_3).

(2R,3S,4R)-4-Methoxybenzyl 2-((S)-((S)-cyclohex-2-en-1-yl)(hydroxy)methyl)-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxopyrrolidine-2-carboxylate 48



To a solution of lactone **47** (200 mg, 0.466 mmol) in THF (8.0 mL) at -10 °C, was added DiBAL-H (1.0 M in hexanes, 2.80 mL, 2.80 mmol) over 5 min. This mixture was stirred for 15 min at -10 °C and was treated with MeOH (15 mL). The mixture was stirred for 5 min at 22 °C and NaBH₄ (880 mg, 50.0 eq) was added in 5 eq. portions every 10 min. The mixture was stirred for 30 min and was quenched with sat. aq. NH₄Cl solution (20 mL). The solution was diluted with EtOAc (120 mL), water (40 mL) and sat. aq. Rochelle's salt solution (100 mL) and the mixture was vigorously stirred for 6 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (50:1 EtOAc:MeOH), which gave triol **48** (139 mg, 0.76 mmol, 69%) as a white solid. **m.p.** 93–96 °C; **R**_f 0.31 (EtOAc); **δ**_H (500 MHz, methanol-*d*₄) 7.39–7.34 (2H, m, ArH), 7.93–7.88 (2H, m, ArH), 5.76–5.70 (2H, m, CH=CH), 5.24 (1H, d, *J* = 11.0, CHHAr), 5.05 (1H, d, *J* = 11.0, CHHAr), 3.91 (1H, d, *J* = 5.0, CHOH), 3.79 (3H, s, OCH₃), 3.73 (2H, t, *J* = 6.3, CH₂OH), 2.89 (1H, dd, *J* = 8.6, 4.5, N(CO)CH), 2.03–1.94 (1H, m, CHCHOH), 1.93–1.86 (2H, m, CH₂CH₂CH₂CH=CH), 1.86–1.80 (1H, m, CHHCH₂OH), 1.78–1.68 (1H, m, CHHCH₂OH), 1.63–1.56 (1H, m, CH₂CHHCH₂CH=CH), 1.57 (3H, s, CCH₃), 1.47–1.37 (1H, m, CHHCH₂CH₂CH=CH), 1.36–1.25 (1H, m, CH₂CHHCH₂CH=CH), 1.23–1.10 (1H, m, CHHCH₂CH₂CH=CH); **δ**_C (126 MHz, methanol-*d*₄) 181.3 (C=O), 171.8 (C=O), 161.4 (Ar), 132.0 (Ar), 130.5 (CH=CH), 128.8 (Ar), 128.1 (CH=CH), 114.9 (Ar), 82.6 (C), 78.9 (C), 76.6 (CHOH), 68.0 (CH₂Ar), 62.1 (CH₂OH), 55.7 (OCH₃), 50.9 (N(CO)CH), 40.4 (CHCHOH), 28.4 (CH₂CH₂CH₂CH=CH), 27.8 (CH₂CH₂OH), 25.9 (CH₂CH₂CH₂CH=CH), 22.9 (CH₂CH₂CH₂CH=CH), 20.4 (CCH₃); **v**_{max} 3298 (br, OH), 2934 (w, C-H), 1716 (m, C=O), 1684 (m, C=O), 1247 (s), 824 (w); **m/z** (ESI⁺) 434 ([M+H]⁺, 100%), 456 ([M+Na]⁺, 30%); HRMS found 456.2006, [C₂₃H₃₁NNaO₇]⁺ requires 456.1993; **[α**_D²⁰ +72.1 (*c* = 1.00, MeOH).

(1*R*,4*R*,5*S*)-4-(2-Chloroethyl)-1-((*S*)-((*S*)-cyclohex-2-en-1-yl)(hydroxy)methyl)-5-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione - *salinosporamide A* 1

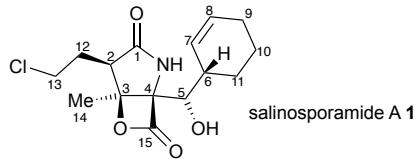


To a solution of triol **48** (75 mg, 0.173 mmol) in DCM (3.5 mL) at 0°C was added BCl_3 (1.0 M in DCM , 0.69 mL, 0.69 mmol) over 5 min. The reaction mixture was stirred for 30 min and was quenched with MeOH (0.2 mL). The mixture plugged through a 2.5 cm silica pad (eluting with 20:1 $\text{DCM}:\text{MeOH}$ 4 CV then 4:1 $\text{DCM}:\text{MeOH}$ 4 CV), which gave the corresponding carboxylic acid (54.2 mg), which was used without further purification.

To a solution of crude carboxylic acid prepared above (54.2 mg) in DCM (1.0 mL) and pyridine (0.50 mL) at 22°C , was added BOPCl (66.2 mg, 0.216 mmol) in one portion. The reaction was stirred for 2 h and another portion of BOPCl (21.0 mg, 0.0720 mmol) was added. After stirring for 1 h the volatiles were removed *in vacuo*. The residue was diluted with EtOAc (10 mL) and washed with 10% aq. NaCl solution (10 mL). The aqueous layer was extracted with EtOAc (2×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*, which gave β -lactone **S4** (50.7 mg), which was used without purification.

To a solution of β -lactone **S4** (50.7 mg) in MeCN (0.35 mL) and pyridine (0.35 mL) at 22°C under Ar was added Ph_3PCL_2 (115 mg, 0.346 mmol) in one portion. The mixture was stirred for 2 h and quenched with H_2O (0.05 mL). The volatiles were removed *in vacuo*. The residue was diluted with EtOAc (10 mL) and washed with 10% aq. NaCl solution (10 mL). The aqueous layer was extracted with EtOAc (2×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (3:2 $\text{EtOAc}:\text{hexane}$), which gave *salinosporamide A* (33.0 mg, 0.105 mmol, 61% over 3 steps) as a white solid. **m.p.** 175–178 $^\circ\text{C}$ (lit.¹³ 168–170 $^\circ\text{C}$); **R_f** 0.59 (1:1 $\text{EtOAc}:\text{hexane}$); δ_{H} (500 MHz, $\text{pyridine}-d_5$) 10.65–10.60 (1H, br, NH), 7.67–7.45 (1H, br, OH), 6.45 (1H, d, J = 10.2, $\text{CHCH}=\text{CHCH}_2$), 5.95–5.86 (1H, m, $\text{CHCH}=\text{CHCH}_2$), 4.27 (1H, d, J = 9.0, CHOH), 4.21–4.10 (1H, m, CHHCl), 4.08–3.99 (1H, m, CHHCl), 3.19 (1H, t, J = 7.0, $\text{N}(\text{CO})\text{CH}$), 2.93–2.81 (1H, m, CHCHOH), 2.57–2.44 (1H, m, CHHCH_2Cl), 2.41–2.26 (2H, m, CHHC_2Cl and $\text{CHHCH}_2\text{CH}_2\text{CH}=\text{CH}$), 2.09 (s, 3H, CH_3), 2.04–1.86 (2H, m, $\text{CH}_2\text{CH}=\text{CH}$), 1.78–1.64 (2H, m, $\text{CHHCH}_2\text{CH}=\text{CH}$ & $\text{CHHCH}_2\text{CH}_2\text{CH}=\text{CH}$), 1.46–1.33 (1H, m, $\text{CHHCH}_2\text{CH}=\text{CH}$); δ_{C} (126 MHz, $\text{pyridine}-d_5$) 176.7 (C=O), 169.2 (C=O), 128.9 ($\text{CH}_2\text{CH}=\text{CH}$), 128.5 ($\text{CH}_2\text{CH}=\text{CH}$), 86.1 (C), 80.1 (C), 70.8 (CHOH), 46.0 ($\text{N}(\text{CO})\text{CH}$), 43.1 (CH_2Cl), 39.1 (CHCHOH), 28.8 ($\text{CH}_2\text{CH}_2\text{Cl}$), 26.3 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 25.2 ($\text{CH}_2\text{CH}=\text{CH}$), 21.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 19.8 (CH_3); ν_{max} 3395 (w, O-H), 1819 (m, C=O), 1696 (s, C=O), 1025 (w) 833 (m); **m/z** (ESI⁺) 336 ([M+Na]⁺, 100%); HRMS found 336.0978, $[\text{C}_{15}\text{H}_{20}^{35}\text{Cl}\text{INaO}_4]^+$ requires 336.0973; $[\alpha]_D^{20}$ -80.4 (c = 0.49, MeOH) (lit.¹³ -72.98, c =0.55, MeOH).

Table 1 Comparison of the ^{13}C NMR data for synthetic salinosporamide (this work) with that of the natural product.



Carbon ^a	δ_{C} Natural salinosporamide A ¹³ (C ₅ D ₅ N) ^b	δ_{C} Synthetic salinosporamide A (125 MHz, C ₅ D ₅ N)	$\delta_{\text{Syn}} - \delta_{\text{Nat}}$
1	176.4	176.7	0.3
2	46.2	46.0	-0.2
3	86.1	86.1	0.0
4	80.2	80.1	-0.1
5	70.9	70.8	-0.1
6	39.2	39.1	-0.1
7	128.4	128.5	-0.1
8	128.8	128.9	0.1
9	25.3	25.2	-0.1
10	21.7	21.5	-0.2
11	26.5	26.3	-0.2
12	29.0	28.8	-0.2
13	43.2	43.1	-0.1
14	20.0	19.8	-0.2
15	169.0	169.2	0.2

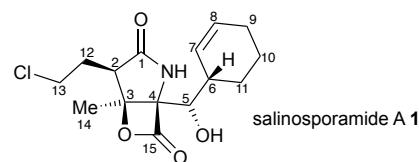
^a Numbering taken from the original isolation paper; ^b unspecified frequency

Table 2 Comparison of the ^{13}C NMR data for synthetic salinosporamide (this work) with data for the synthetic material reported by Danishefsky¹²

Carbon ^a	δ_{C} Salinosporamide A Danishefsky ¹² (125 MHz, C ₅ D ₅ N)	δ_{C} salinosporamide A Burton (125 MHz, C ₅ D ₅ N)	$\delta_{\text{Burton}} - \delta_{\text{Danishefsky}}$
1	176.9	176.7	-0.2
2	46.2	46.0	-0.2
3	86.3	86.1	-0.2
4	80.4	80.1	-0.3
5	80.0	70.8	-0.2
6	39.3	39.1	-0.2
7	128.7	128.5	-0.2
8	129.1	128.9	-0.2
9	25.4	25.2	-0.2
10	21.7	21.5	-0.2
11	26.5	26.3	-0.2
12	29.0	28.8	-0.2
13	43.3	43.1	-0.2
14	20.0	19.8	-0.2
15	169.4	169.2	-0.2

^a Numbering taken from the original isolation paper

Table 3 Comparison of the ^1H NMR data for synthetic salinosporamide (this work) with that of the natural product.



Proton ^a	δ_{C} Natural salinosporamide A ¹³ (C ₅ D ₅ N) ^b	δ_{C} Synthetic salinosporamide A (500 MHz, C ₅ D ₅ N)
2	3.17, t, <i>J</i> 7.0	3.19, t, <i>J</i> 7.0
5	4.24, d, <i>J</i> 9.0	4.27, d, <i>J</i> 9.0
6	2.85, m	2.93-2.81, m
7	6.42, d, <i>J</i> 9.6	6.45, d, <i>J</i> 10.2
8	5.88, m	5.95-5.86, m
9	1.91, m, 2H	1.95, m, 2H
10	1.66, m 1.38, m	1.71, m 1.39, m
11	2.37, m 1.66, m	2.33, m 1.71, m
12	2.48, m 2.32, m	2.57-2.44, m 2.41-2.26, m
13	4.14, m 4.01, m	4.21-4.10, m 4.08-3.99, m
14	2.07, s, 3H	2.09, s, 3H
NH	10.60, br s	10.65-10.60, br s
OH	4.99, br s	7.67-7.45 br s

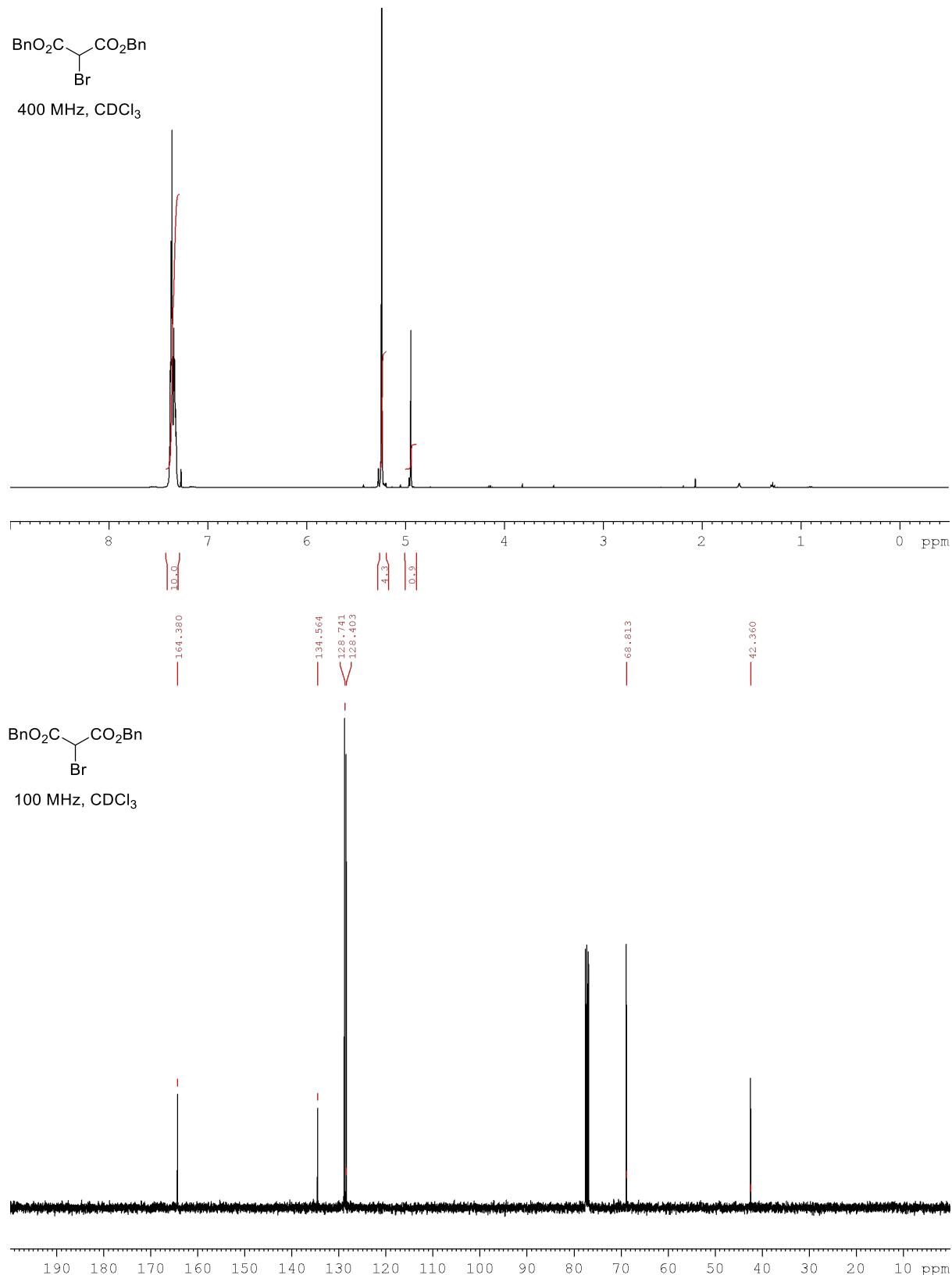
^a Numbering taken from the original isolation paper

References

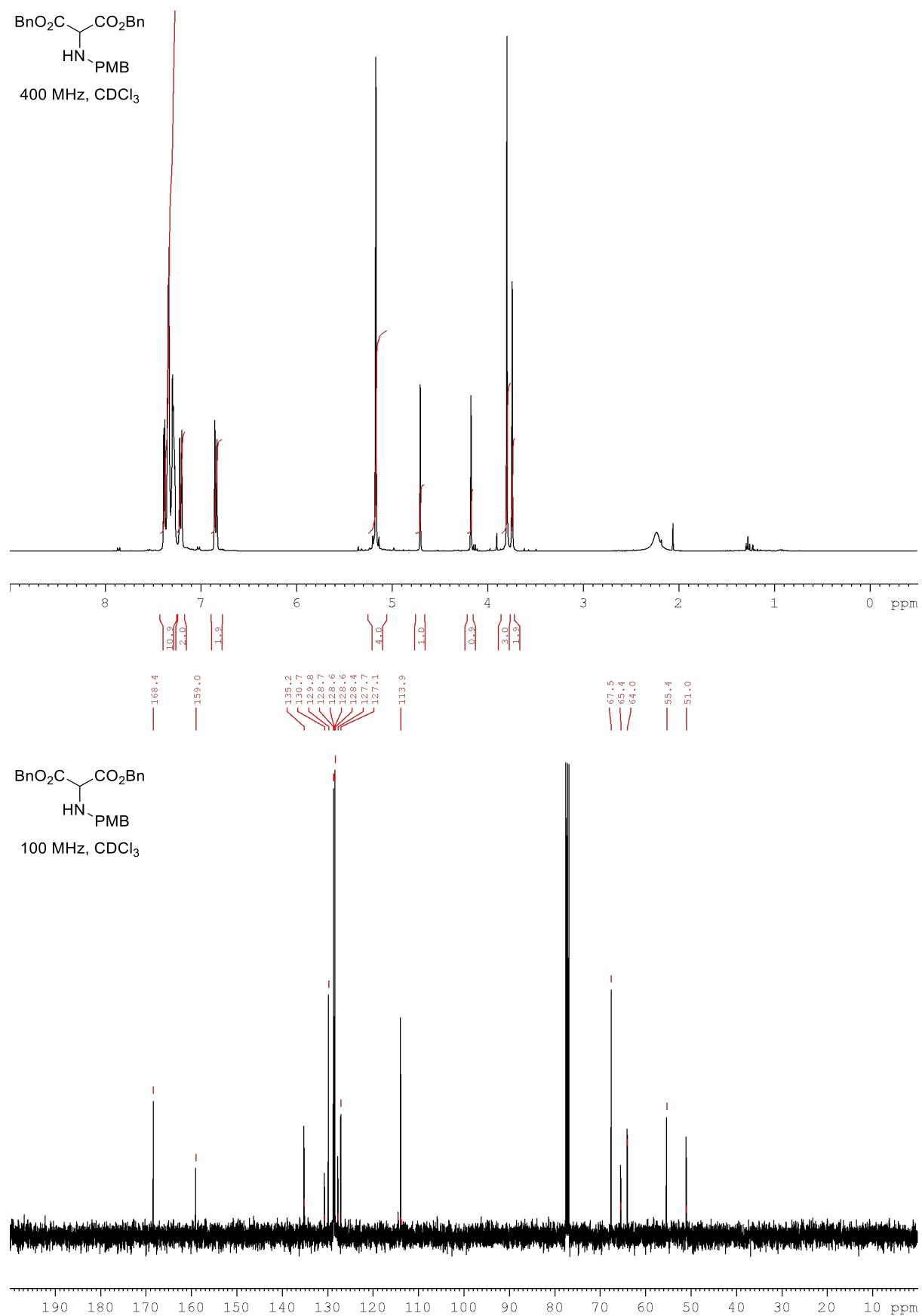
1. A. W. J. Logan, S. J. Sprague, R. W. Foster, L. B. Marx, V. Garzya, M. S. Hallside, A. L. Thompson and J. W. Burton, *Org. Lett.*, 2014, **16**, 4078-4081.
2. S. A. MacDonald, C. G. Willson, M. Chorev, F. S. Vernacchia and M. Goodman, *J. Med. Chem.*, 1980, **23**, 413-420.
3. T. Yamakawa, E. Ideue, Y. Iwaki, A. Sato, H. Tokuyama, J. Shimokawa and T. Fukuyama, *Tetrahedron*, 2011, **67**, 6547-6560.
4. B. Liang, P. J. Carroll and M. M. Joullié, *Org. Lett.*, 2000, **2**, 4157-4160.
5. P. Kocienski, P. Raubo, J. K. Davis, F. T. Boyle, D. E. Davies and A. Richter, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1797-1808.
6. S. Perreault and C. Spino, *Org. Lett.*, 2006, **8**, 4385-4388.
7. S. Wolfe, S. Ro, C.-K. Kim and Z. Shi, *Can. J. Chem.*, 2001, **79**, 1238-1258.
8. W. Hess and J. W. Burton, *Chem. Eur. J.*, 2010, **16**, 12303-12306.
9. W. Oppolzer, R. Moretti and S. Thomi, *Tetrahedron Lett.*, 1989, **30**, 5603-5606.
10. J. R. Dunetz, Y. Xiang, A. Baldwin and J. Ringling, *Org. Lett.*, 2011, **13**, 5048-5051.
11. V. Rodeschini, J.-G. Boiteau, P. Van de Weghe, C. Tarnus and J. Eustache, *J. Org. Chem.*, 2004, **69**, 357-373.
12. A. Endo and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2005, **127**, 8298-8299.
13. R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen and W. Fenical, *Angew. Chem. Int. Ed.*, 2003, **42**, 355-357.

Spectra and HPLC Data

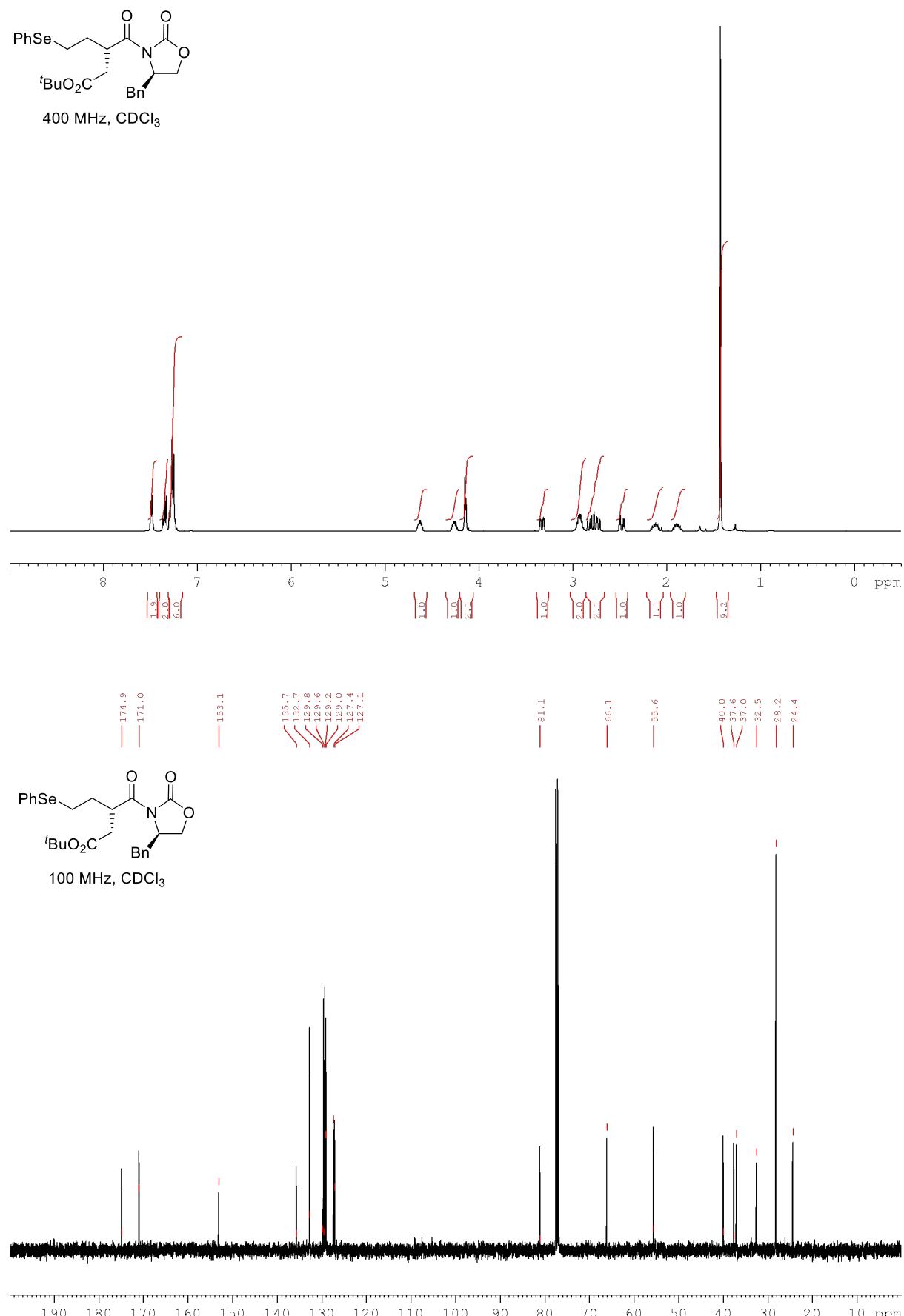
Spectra for compound **S2**



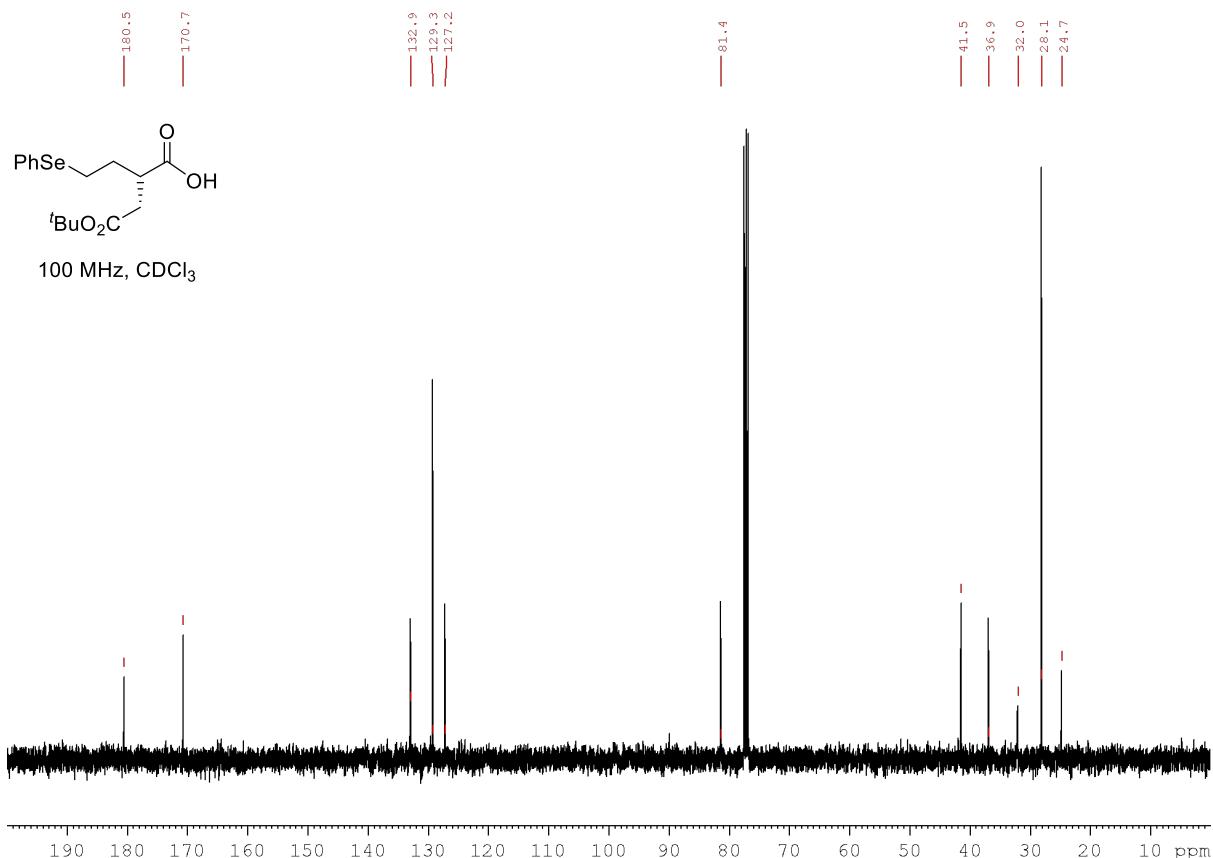
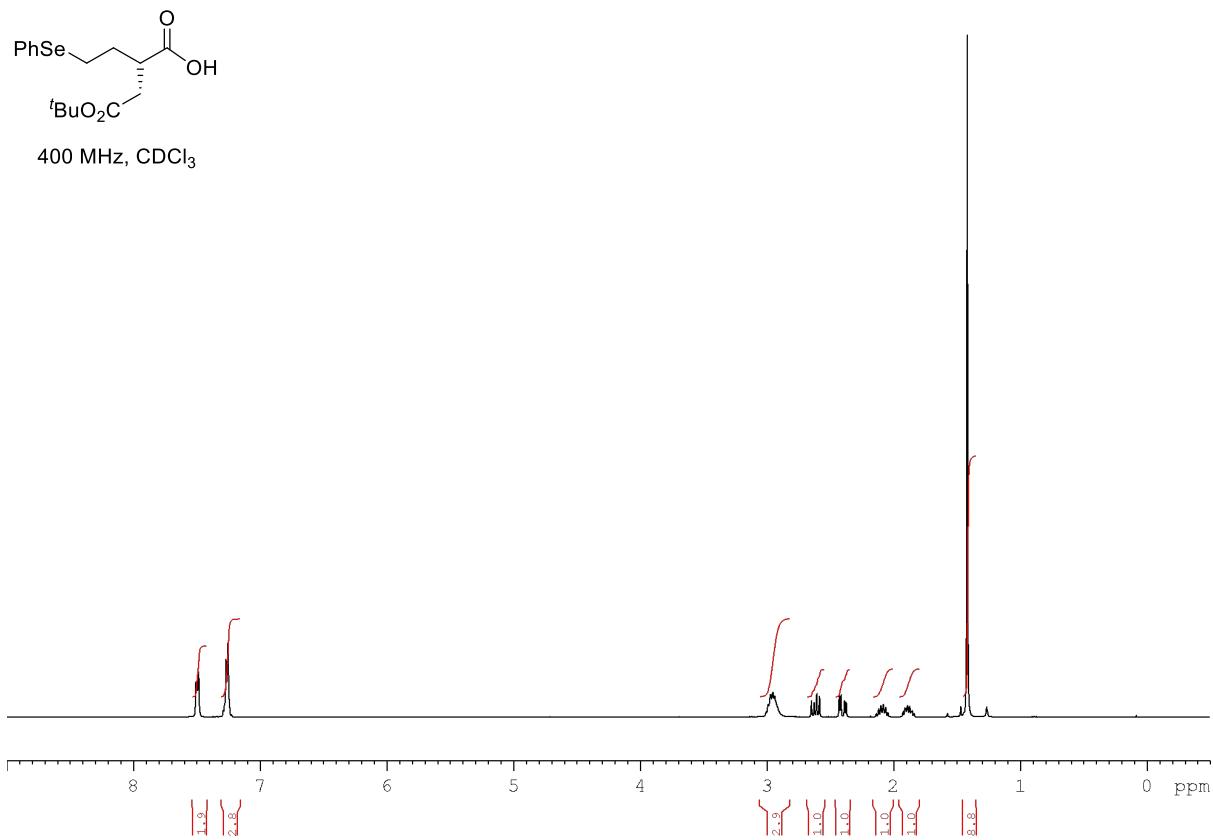
Spectra for compound **16**



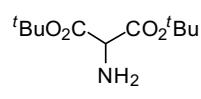
Spectra for compound **13**



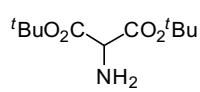
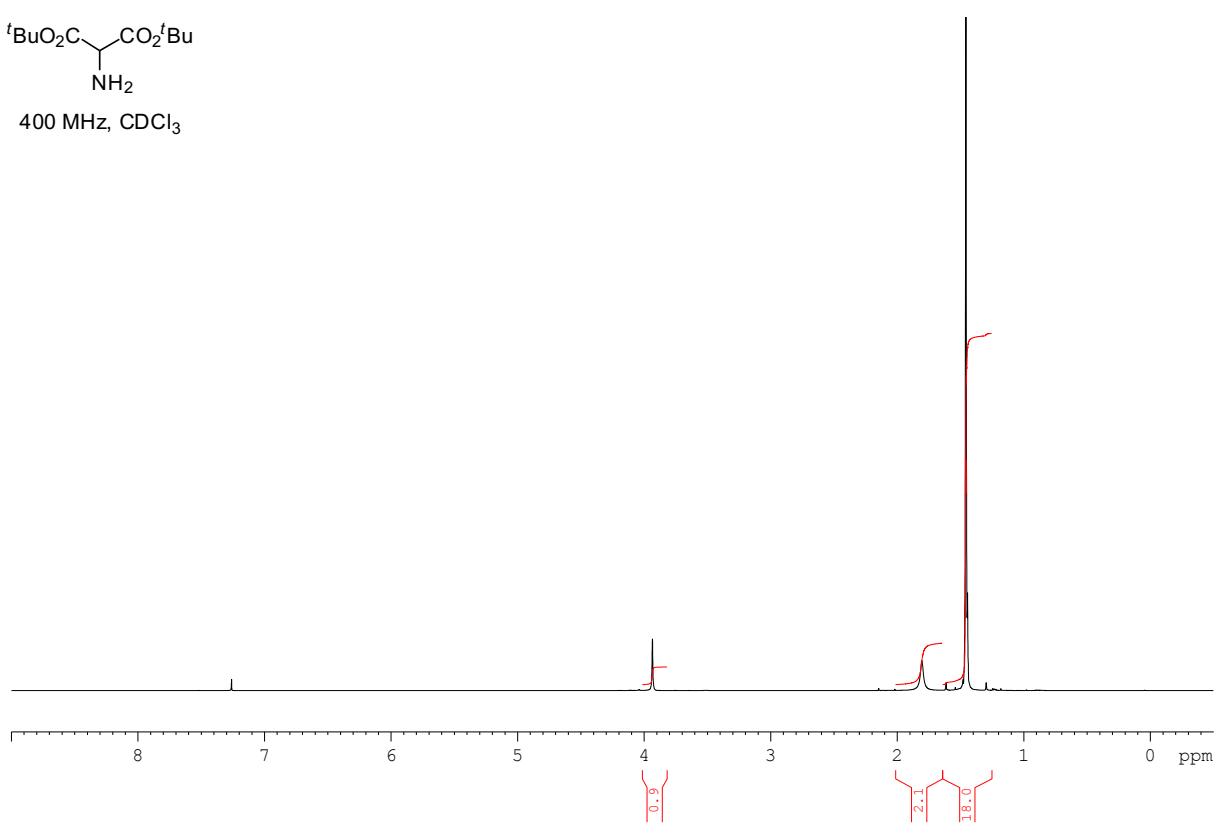
Spectra for compound **14**



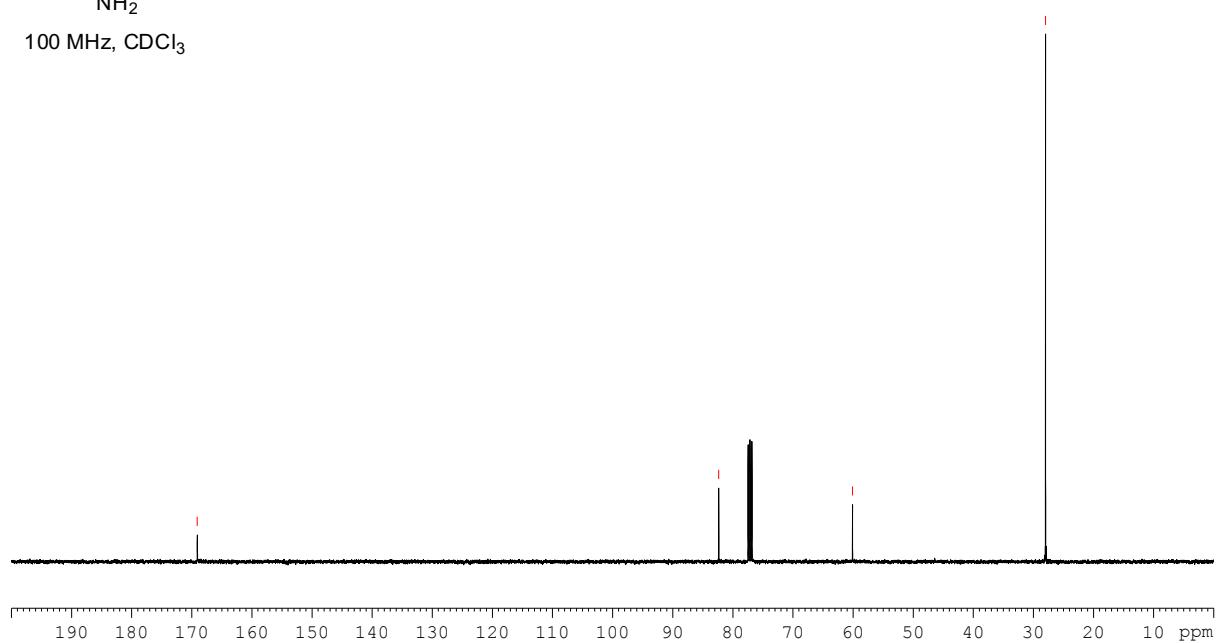
Spectra for compound **34**



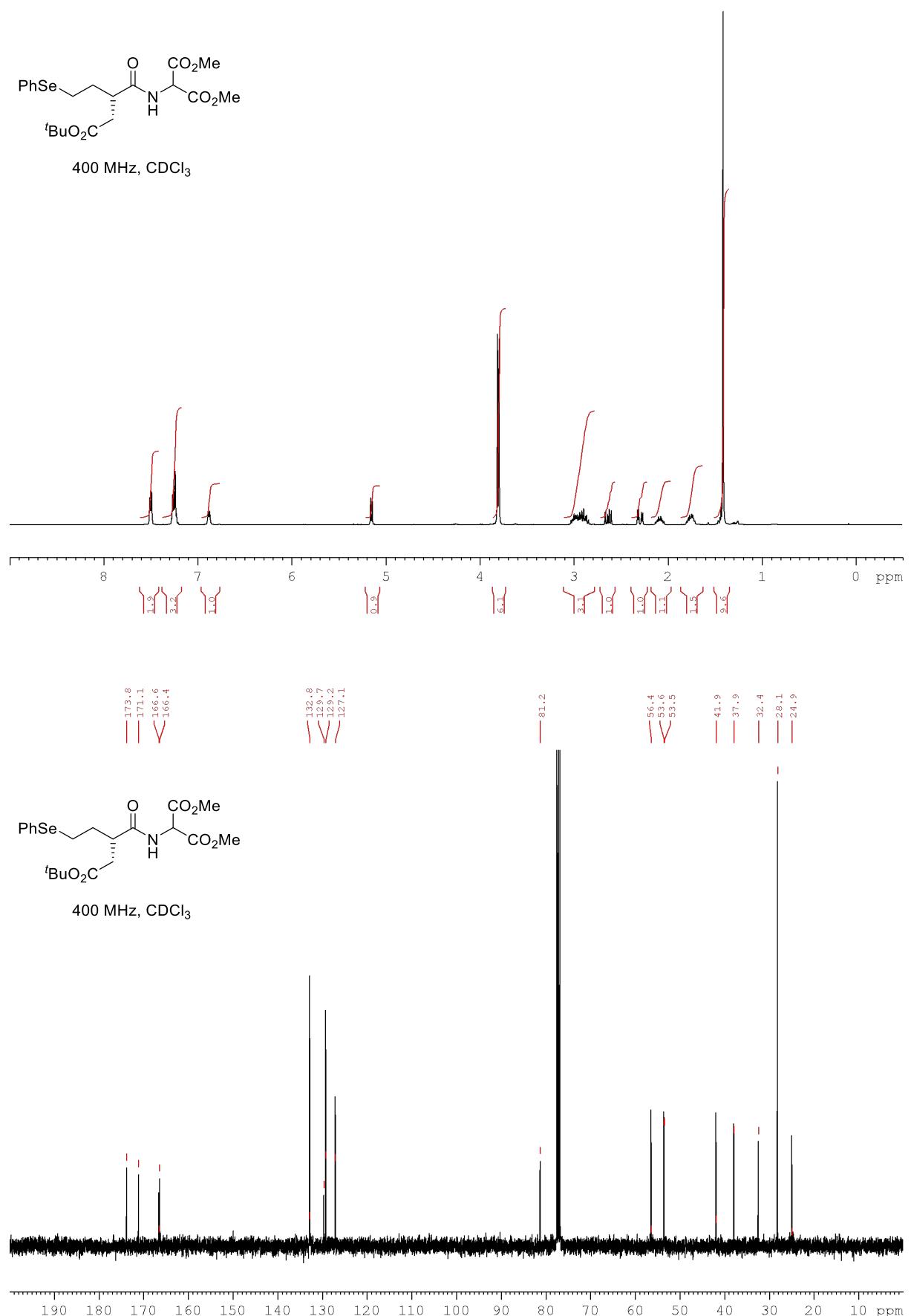
400 MHz, CDCl_3



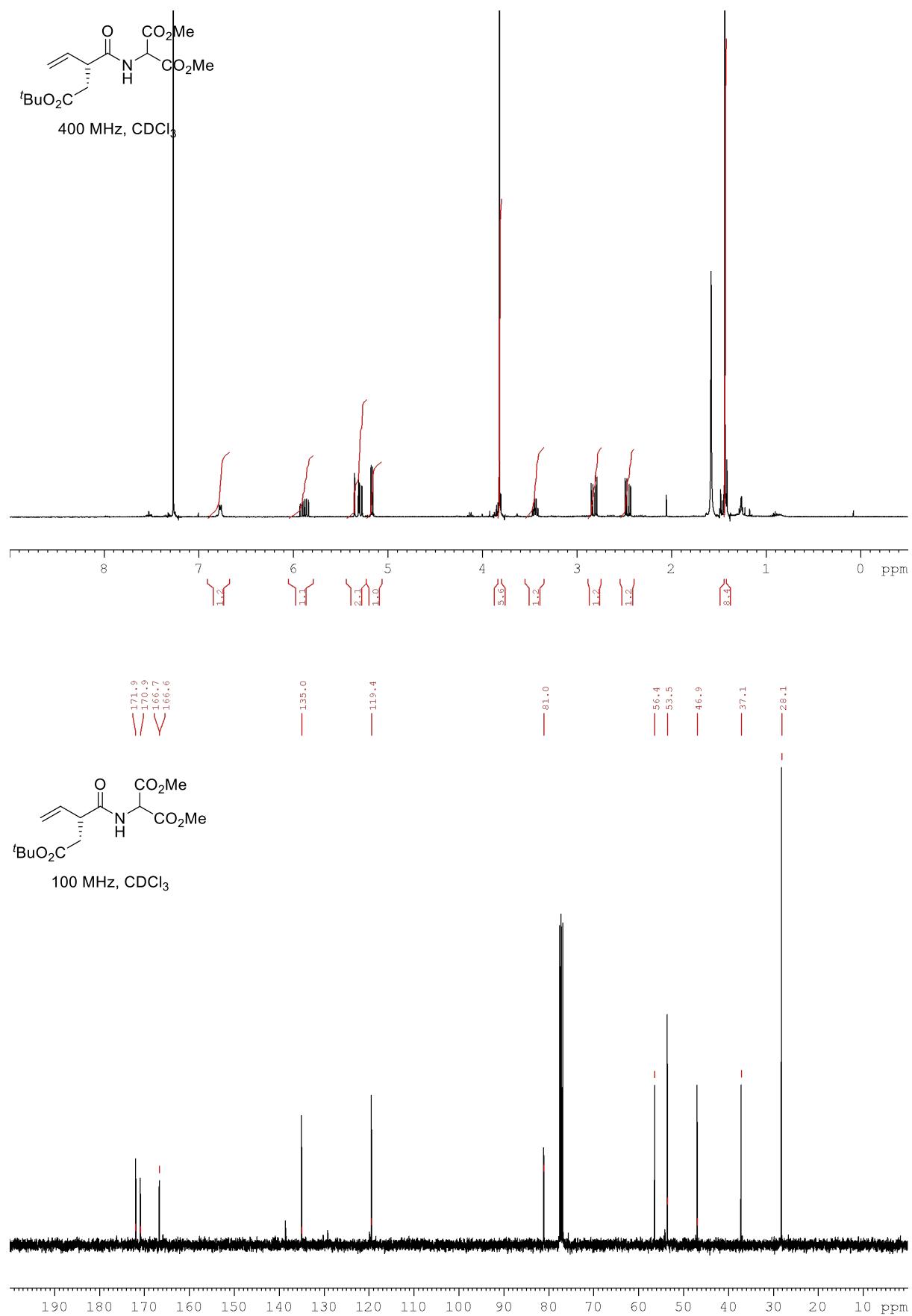
100 MHz, CDCl_3



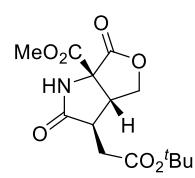
Spectra for compound **19**



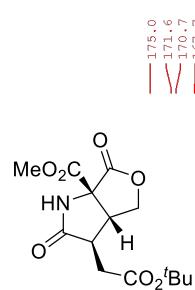
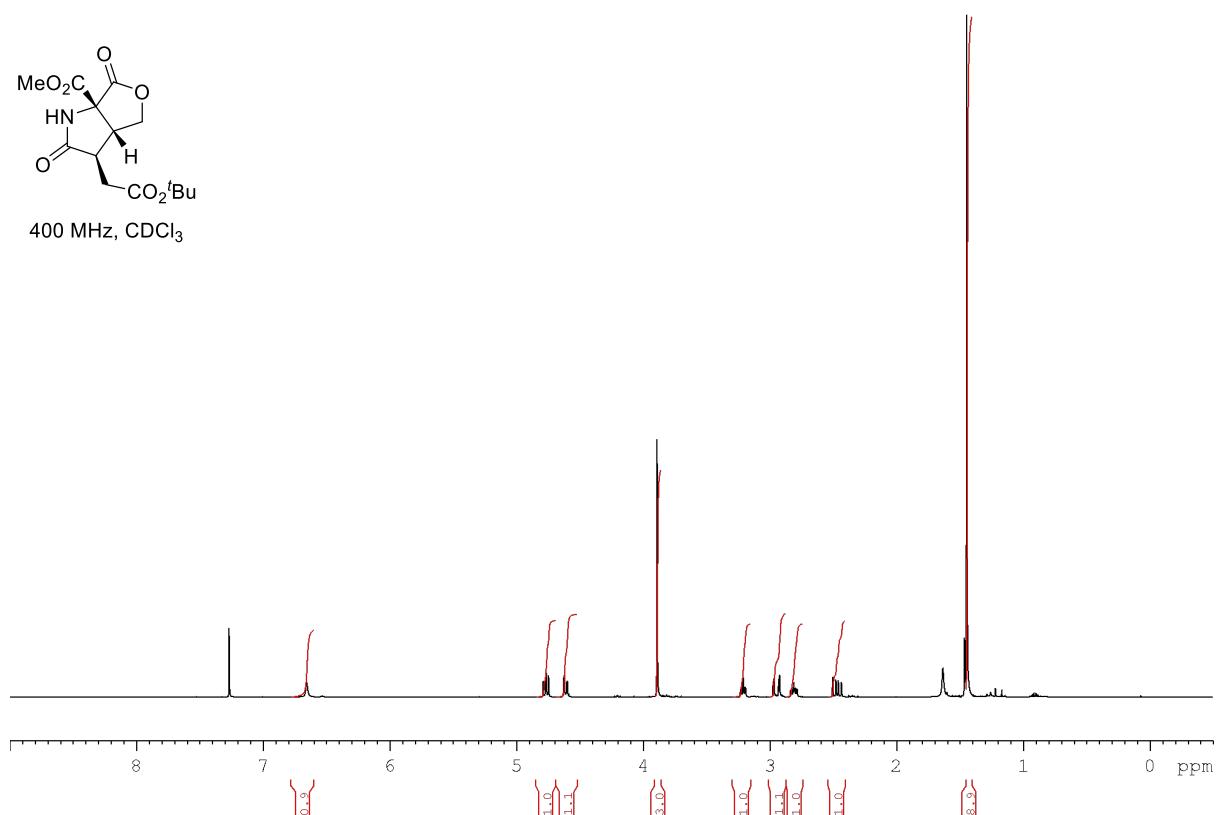
Spectra for compound **20**



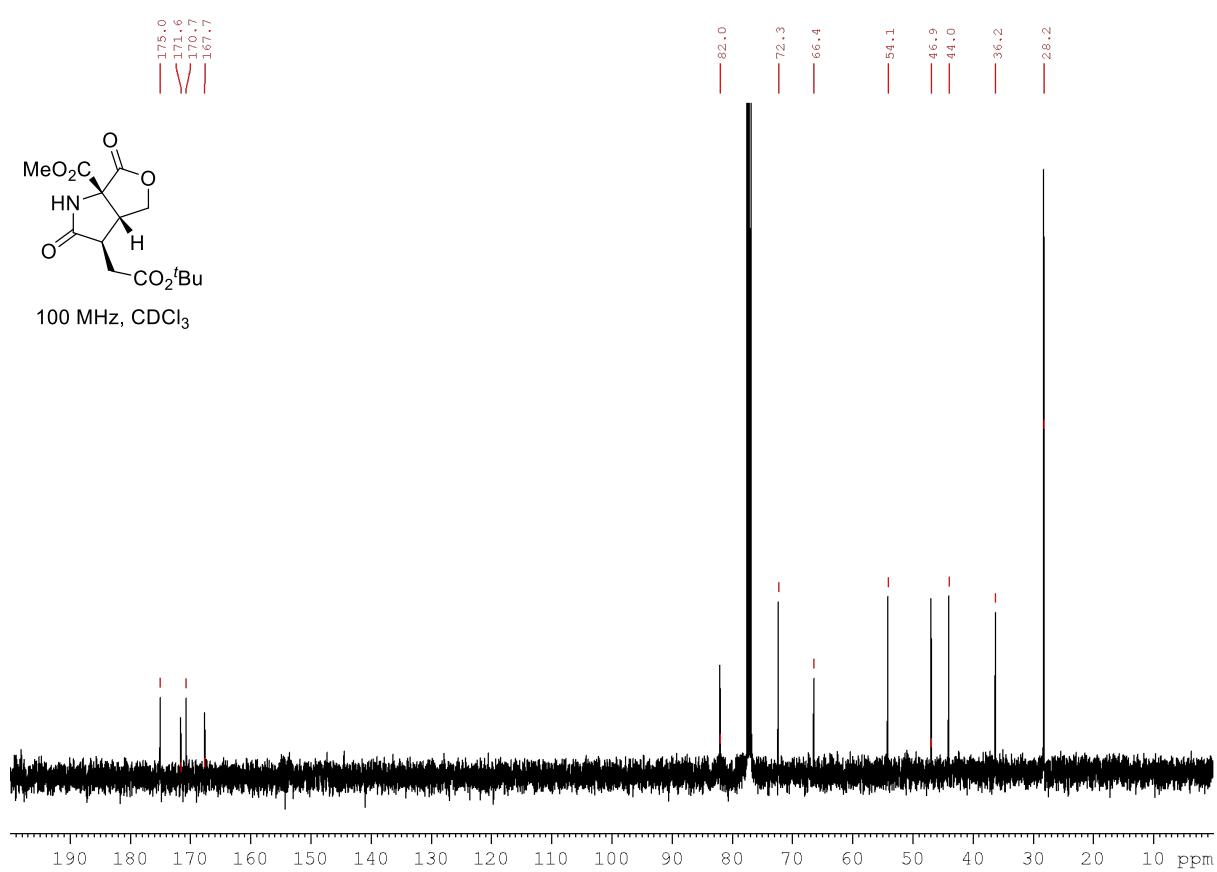
Spectra for compound 23a



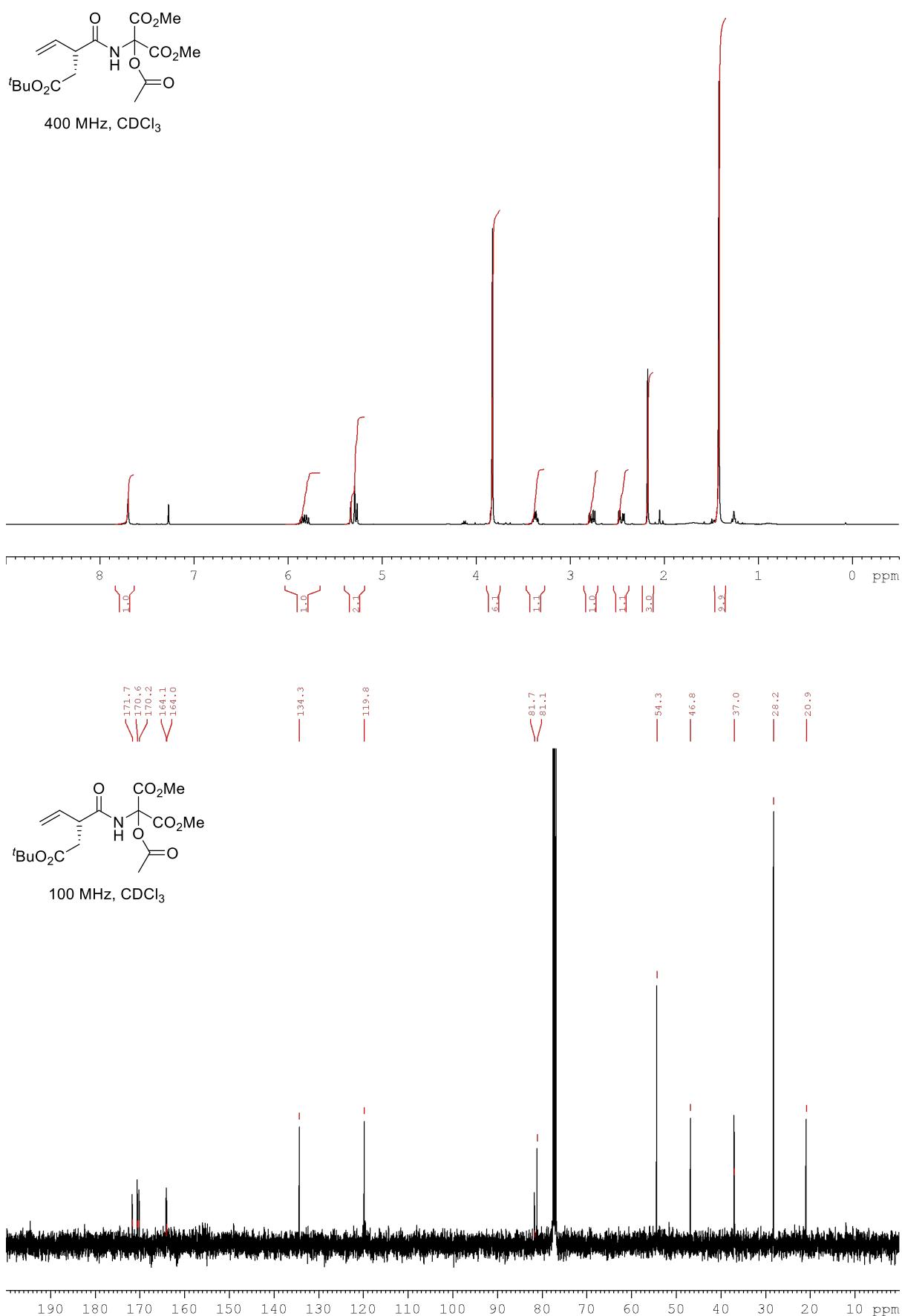
400 MHz, CDCl₃



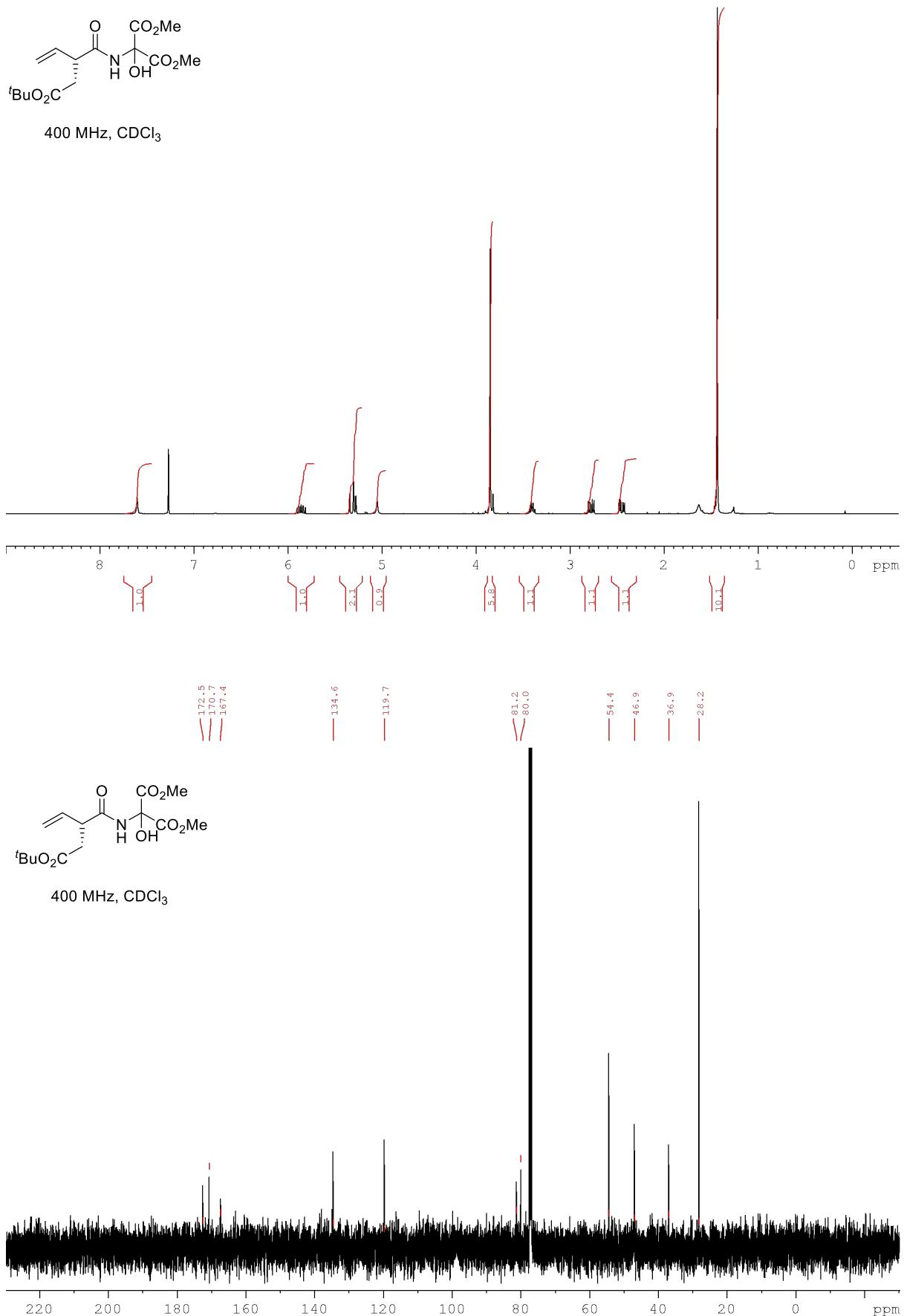
100 MHz, CDCl₃



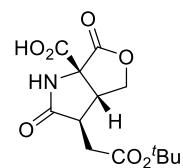
Spectra for compound **22**



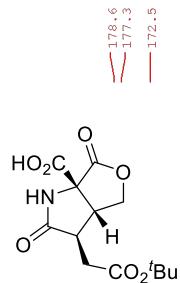
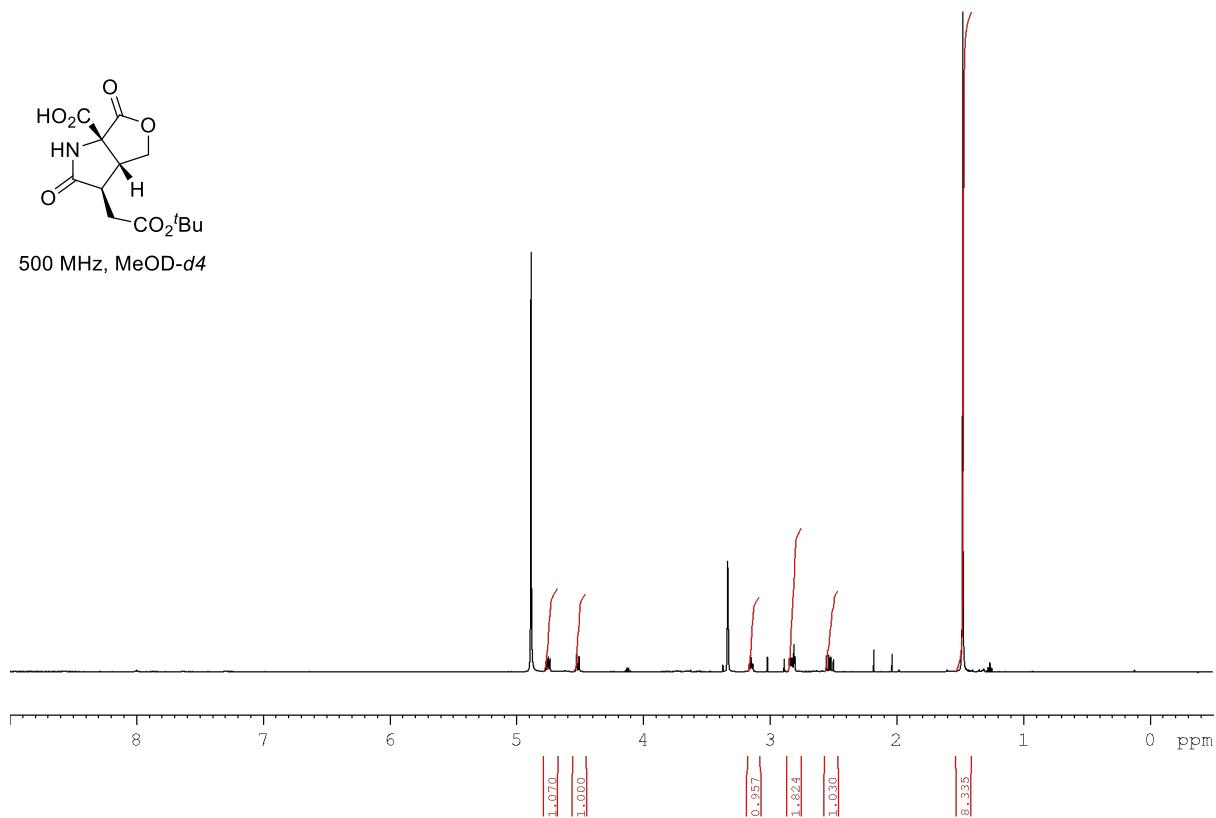
Spectra for compound **21**



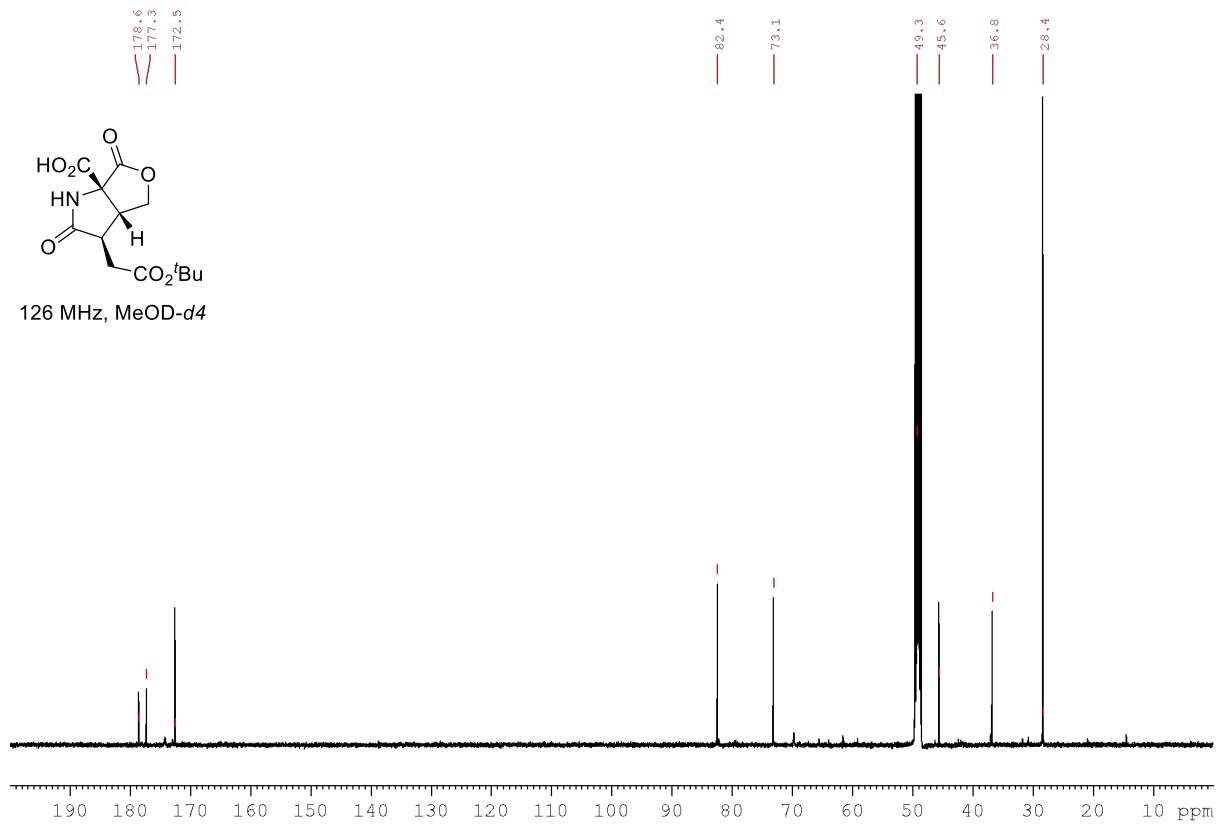
Spectra for compound 24



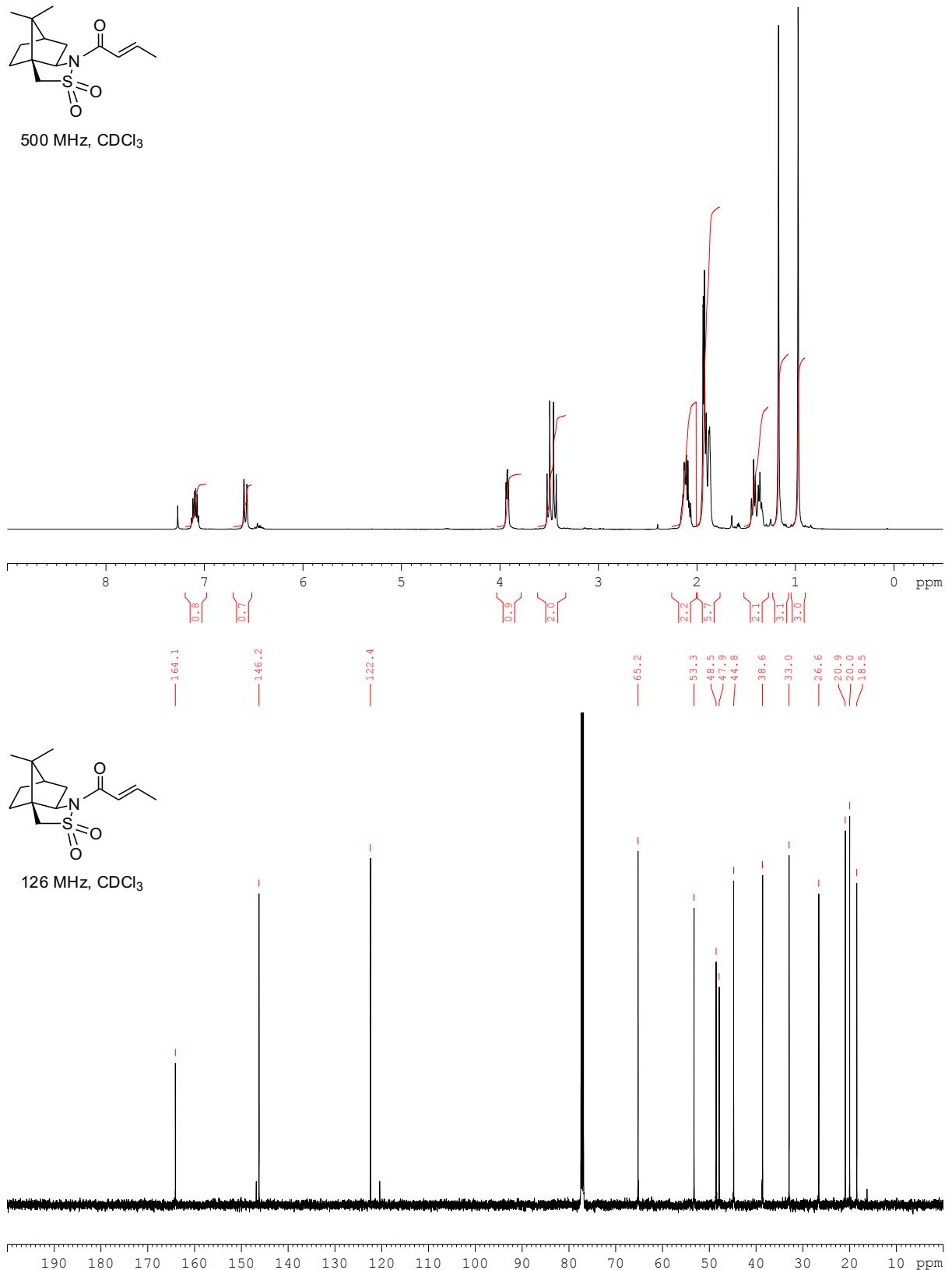
500 MHz, MeOD-*d*4



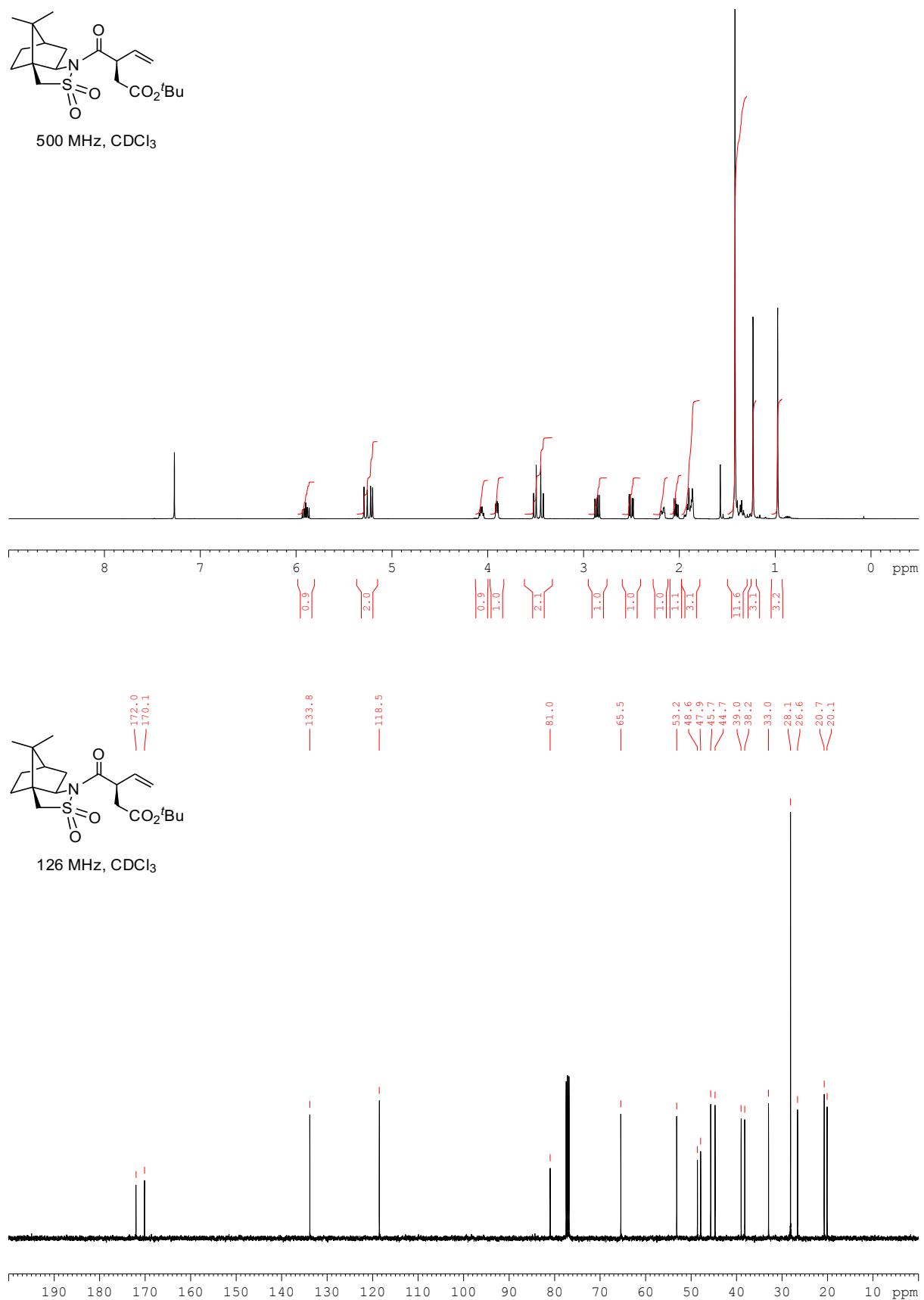
126 MHz, MeOD-*d*4



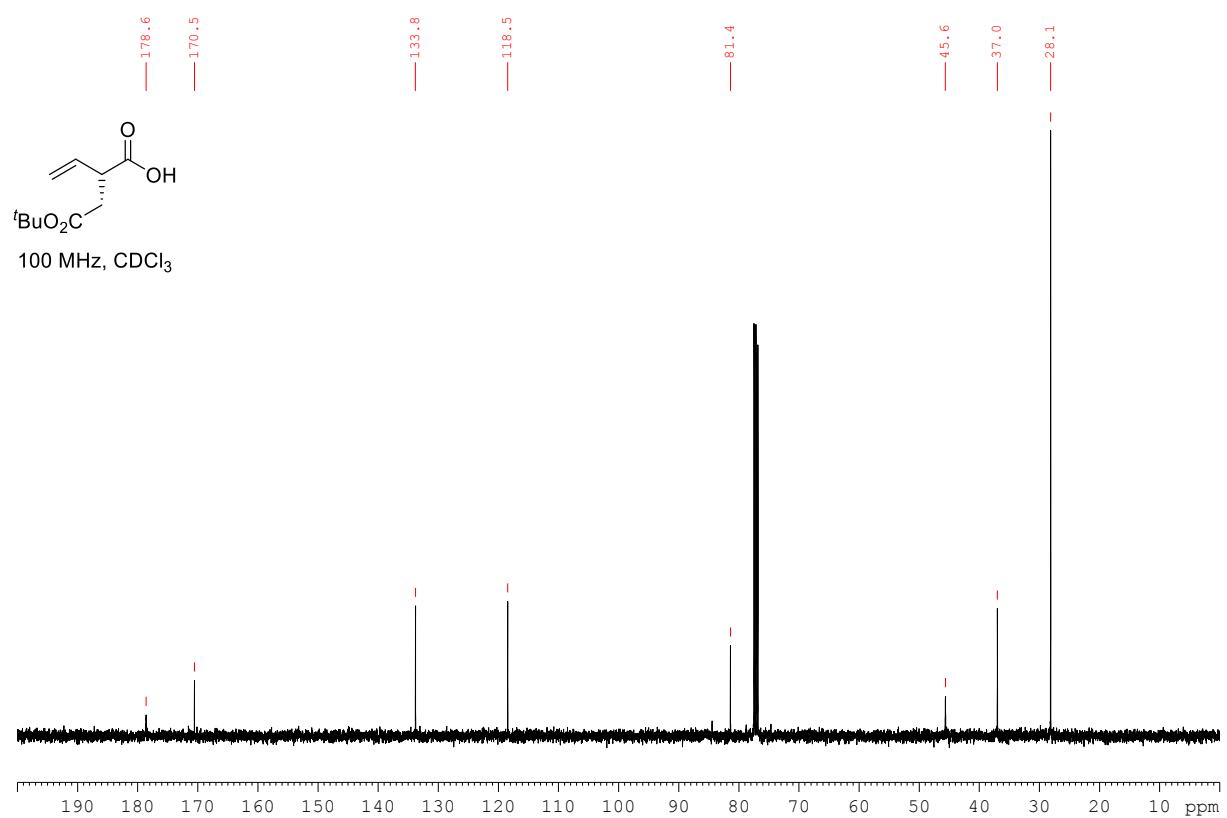
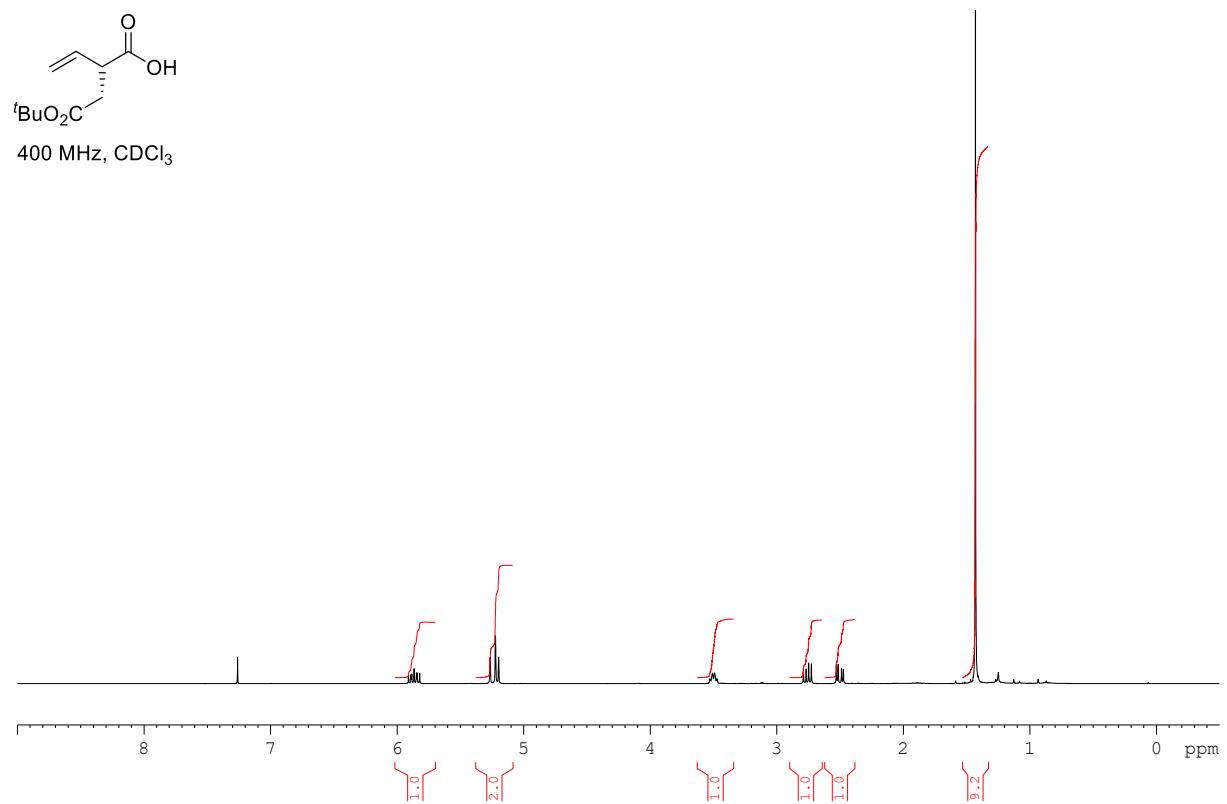
Spectra for compound 31



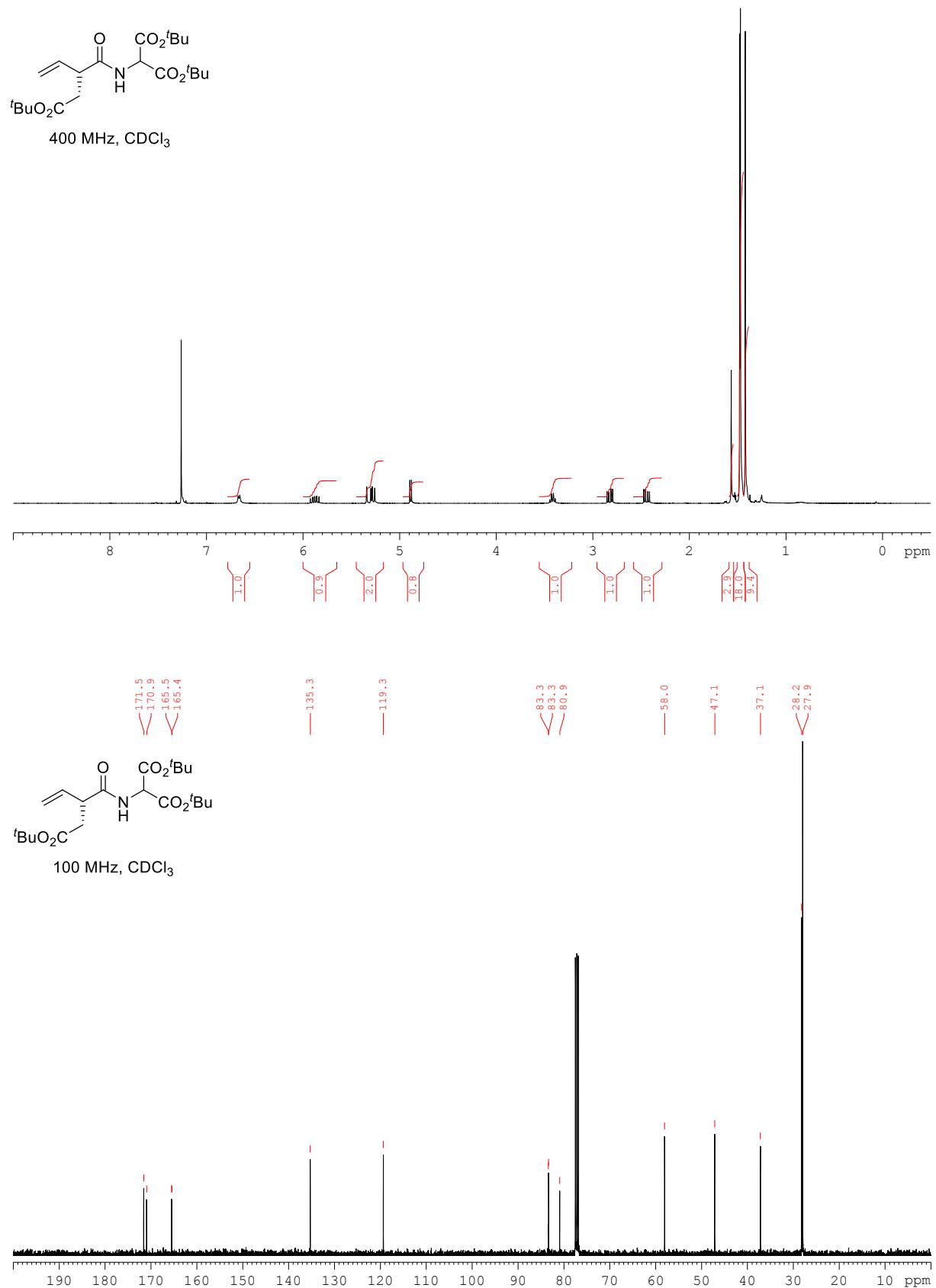
Spectra for compound **32**



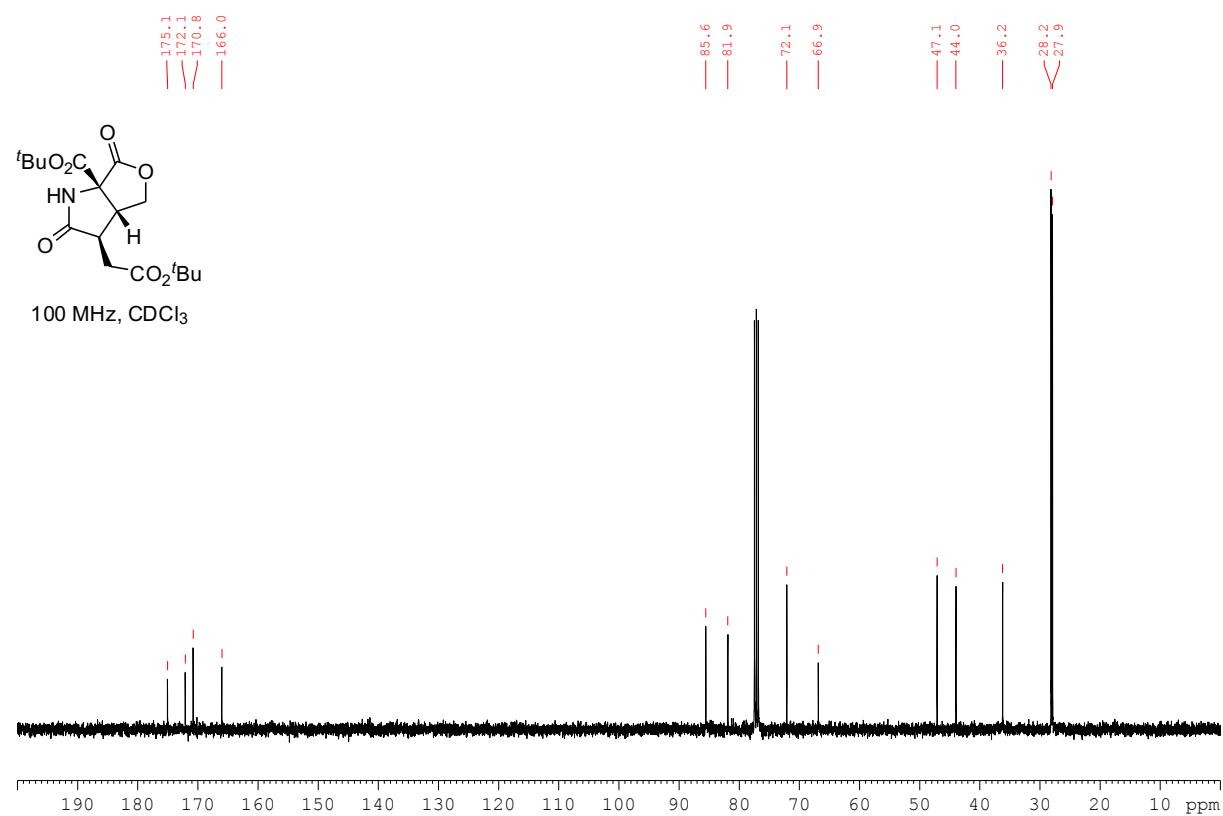
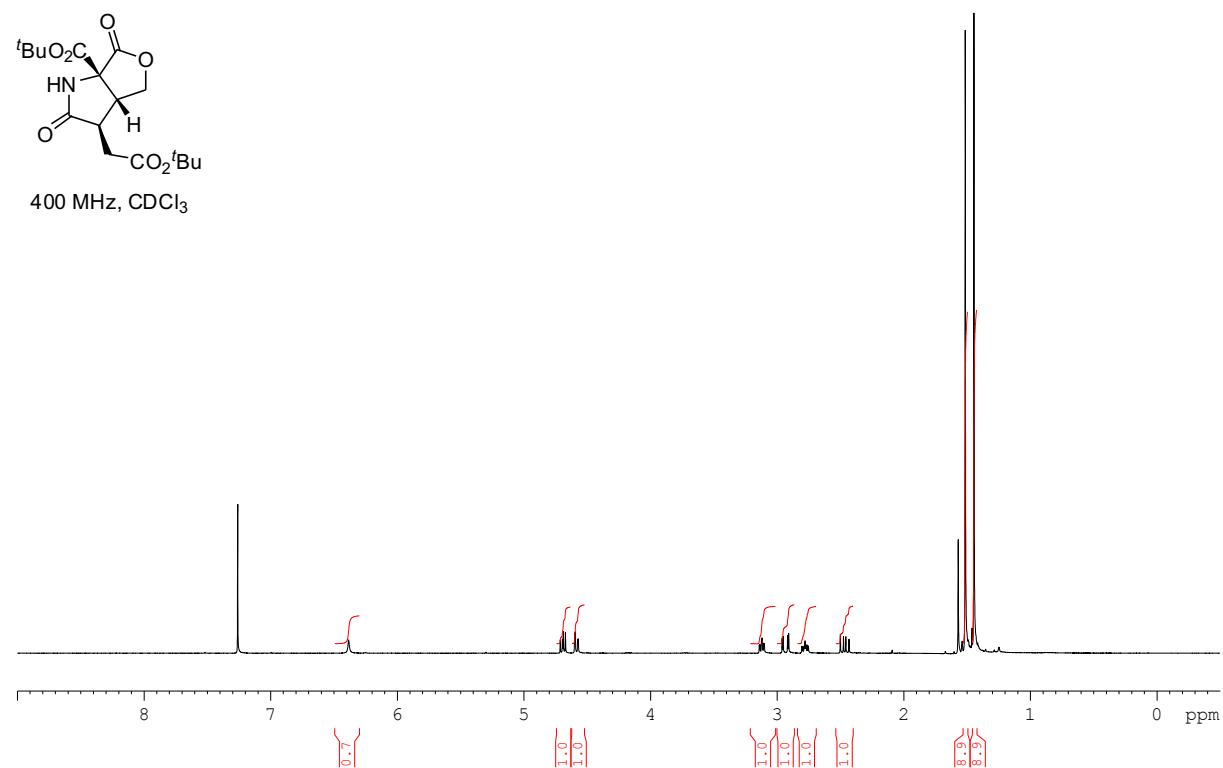
Spectra for compound **33**



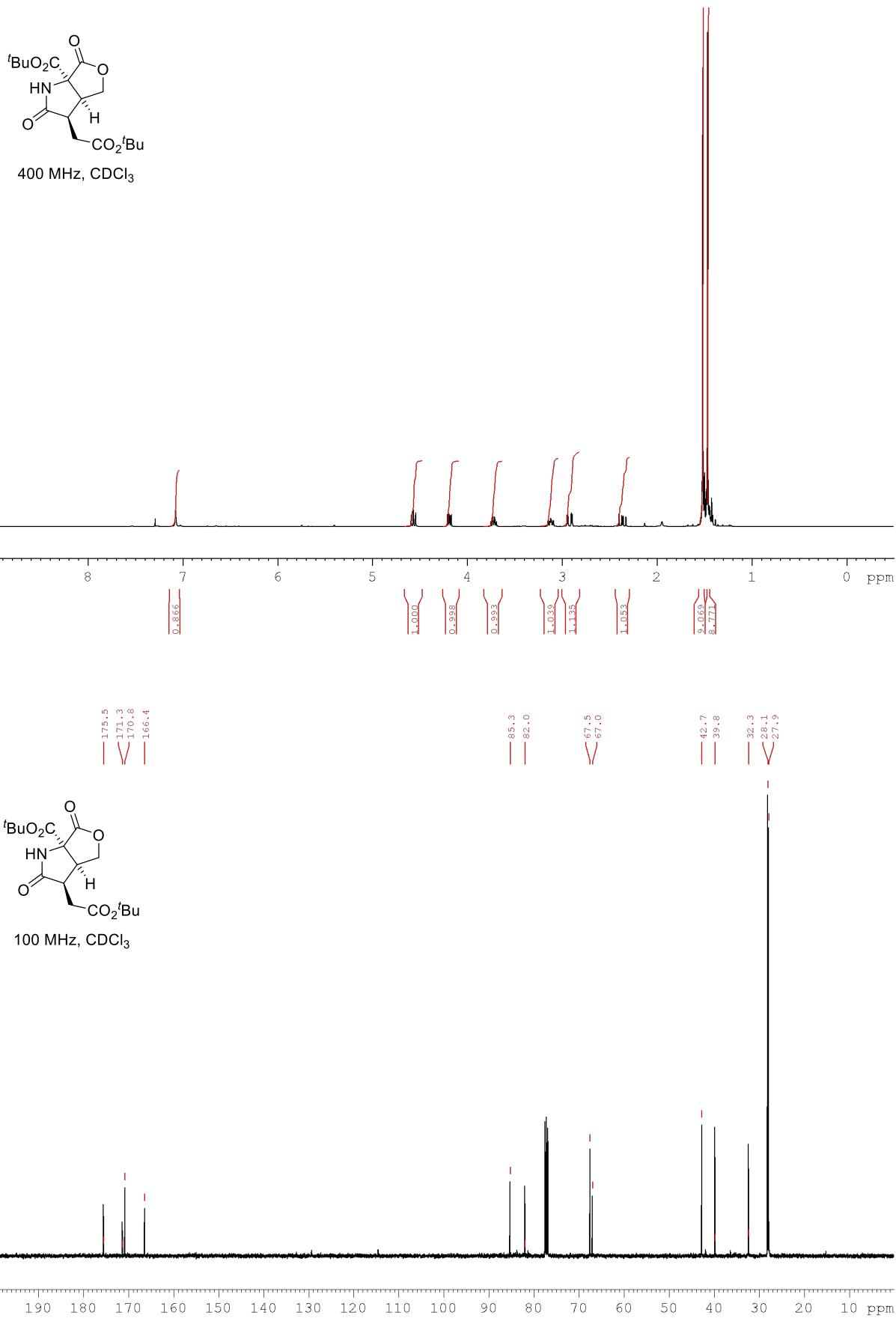
Spectra for compound 35



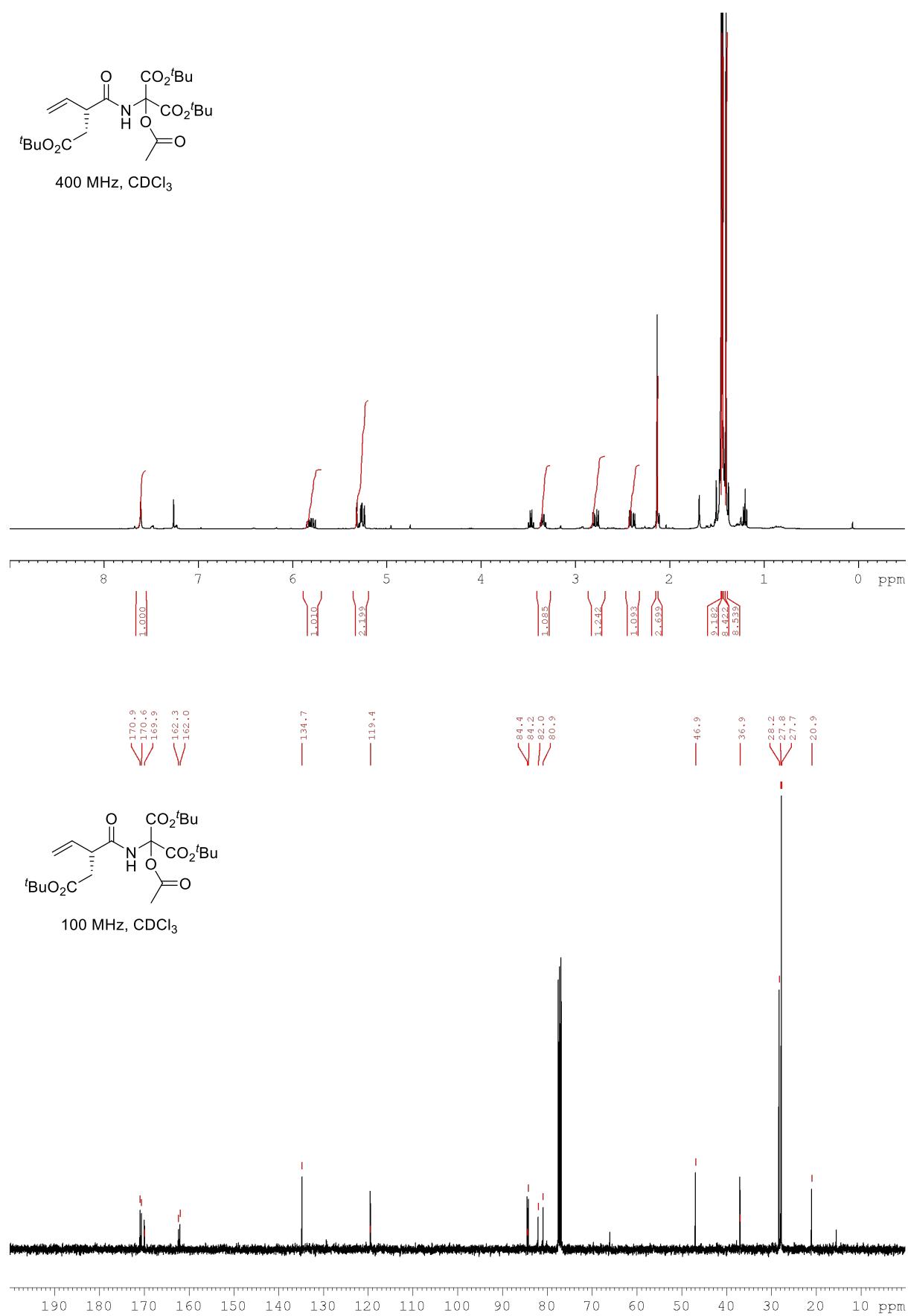
Spectra for compound (+)-36



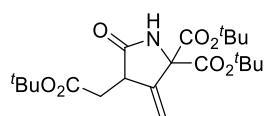
Spectra for compound **S4**



Spectra for compound **38**

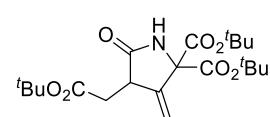
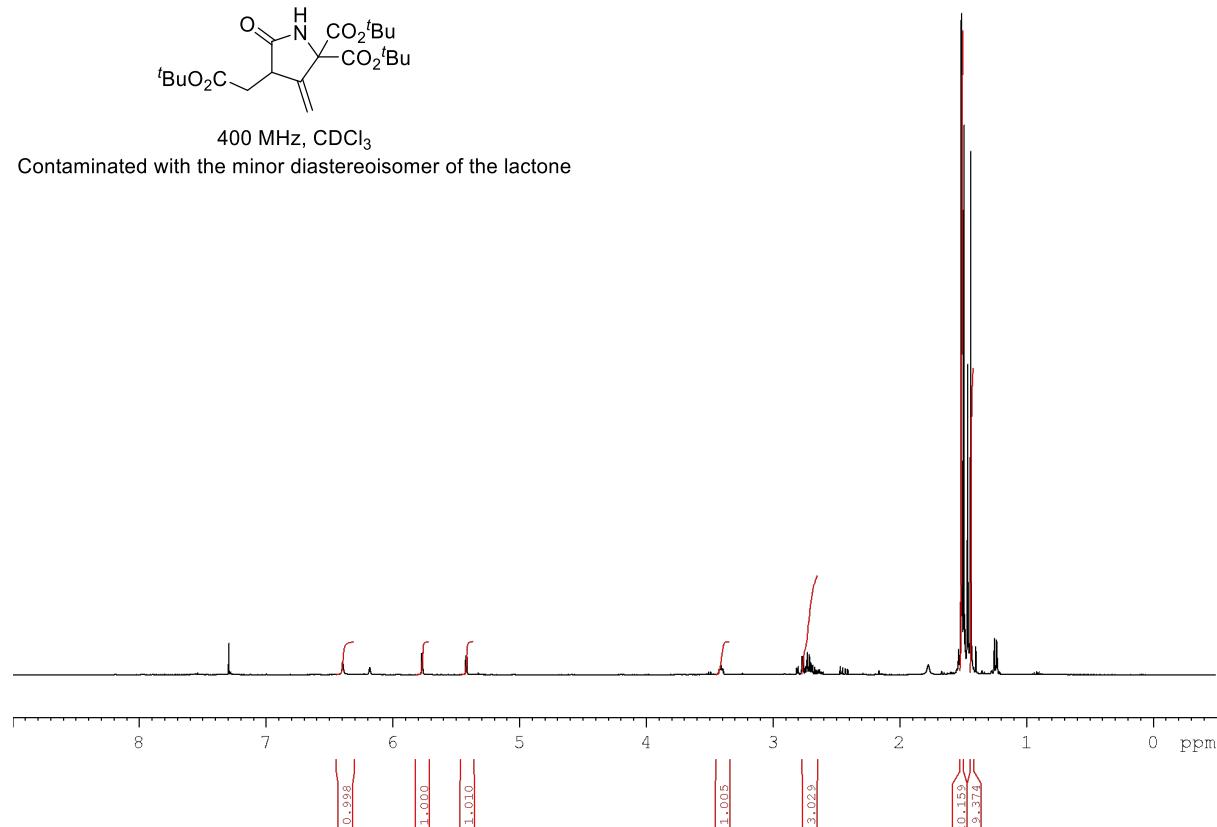


Spectra for compound (\pm)-37



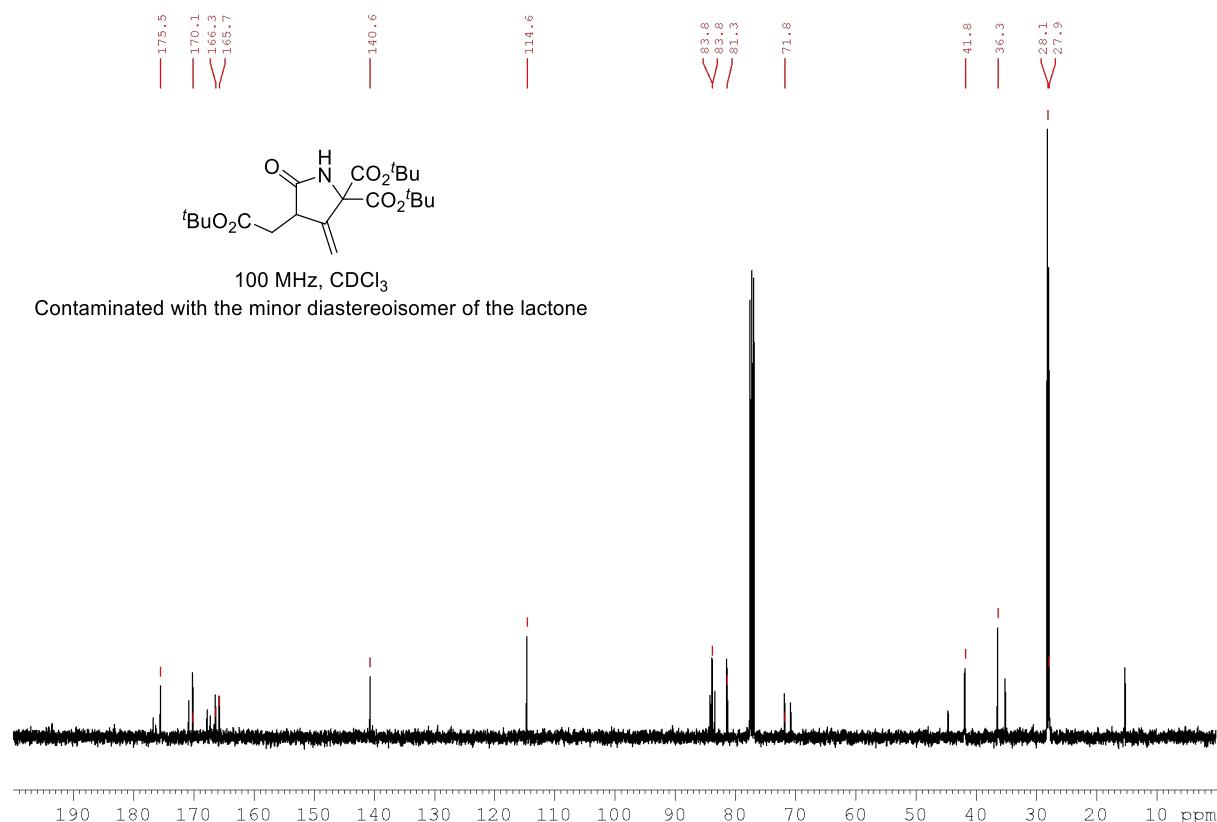
400 MHz, CDCl₃

Contaminated with the minor diastereoisomer of the lactone

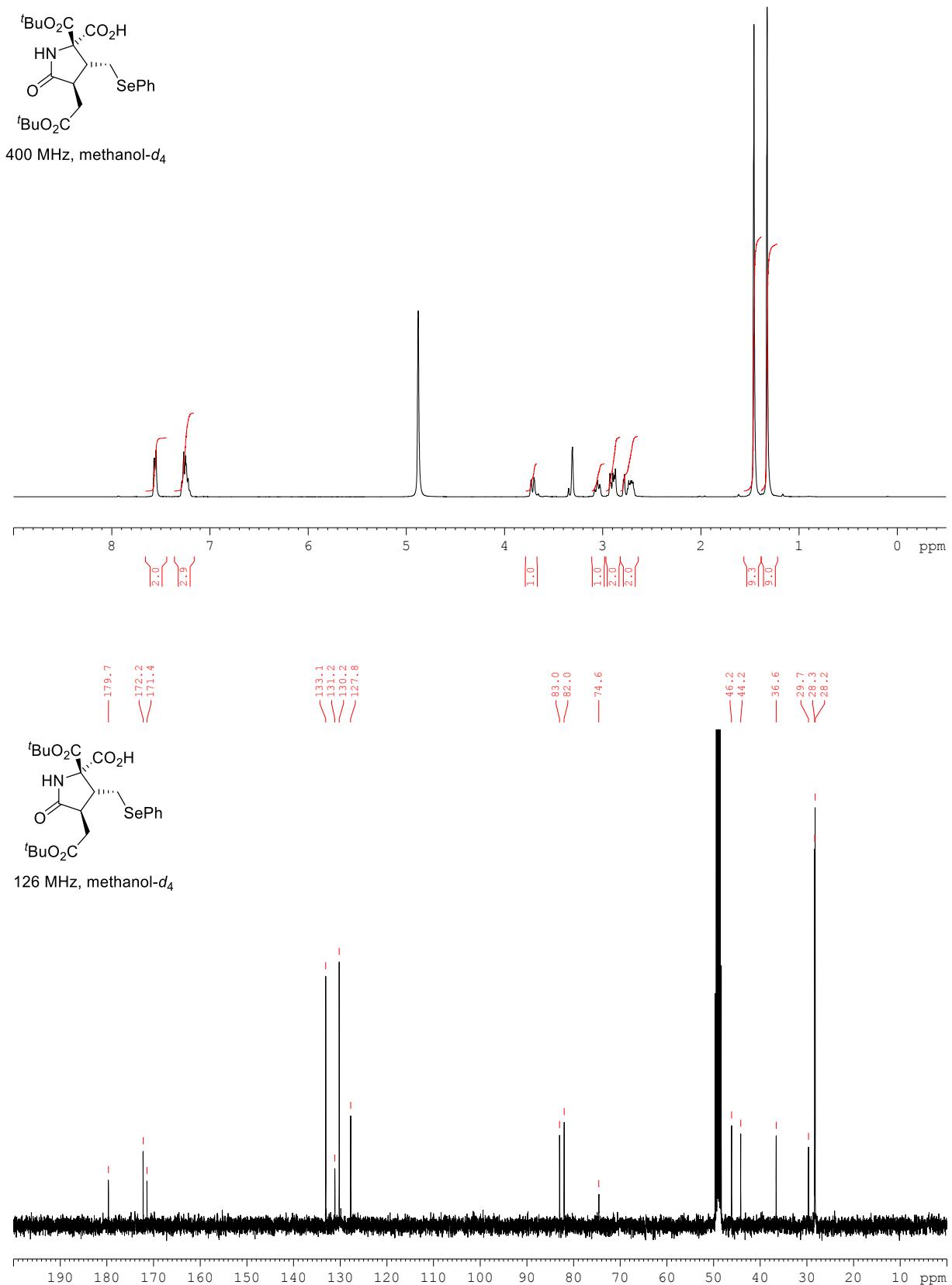


100 MHz, CDCl₃

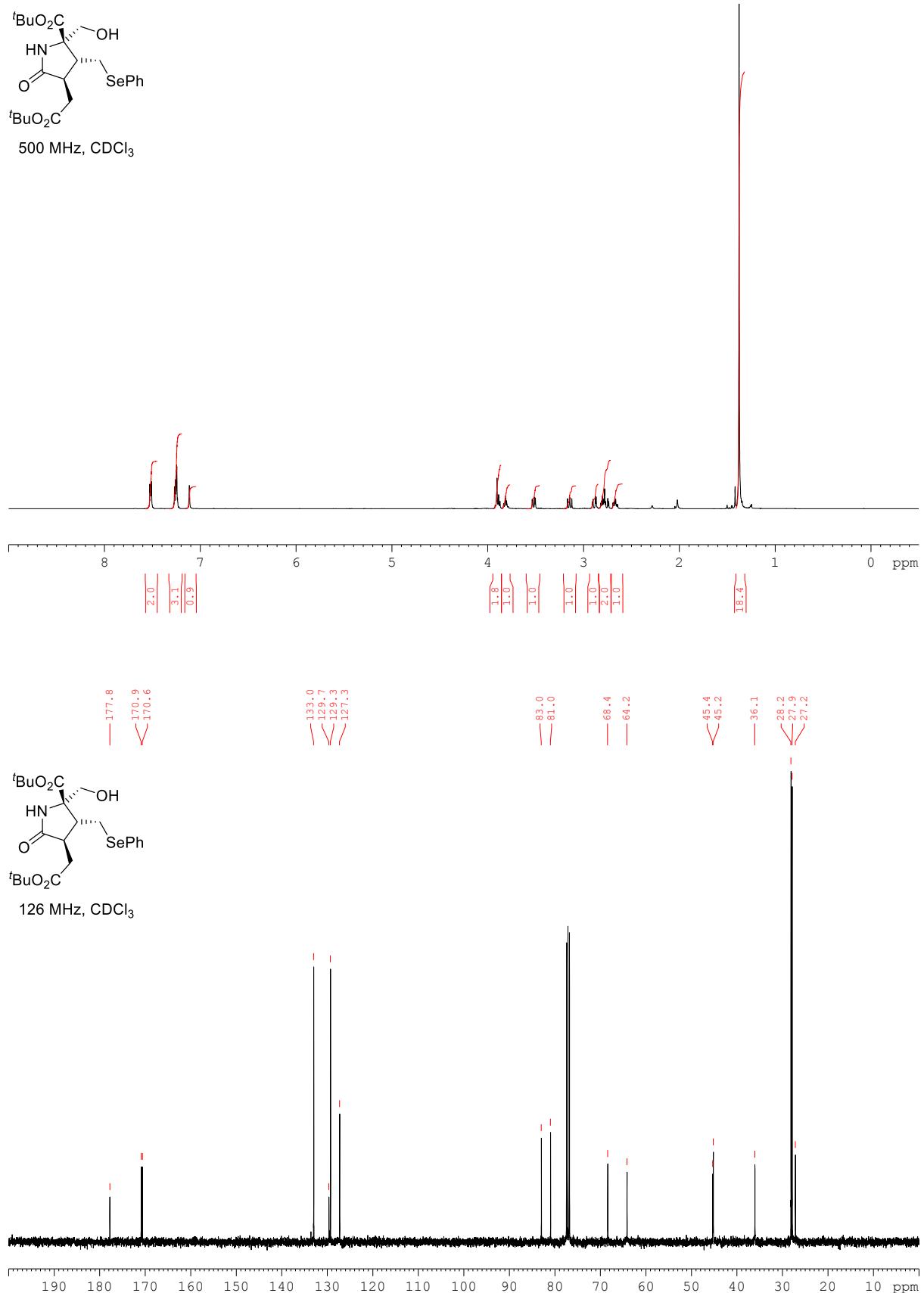
Contaminated with the minor diastereoisomer of the lactone



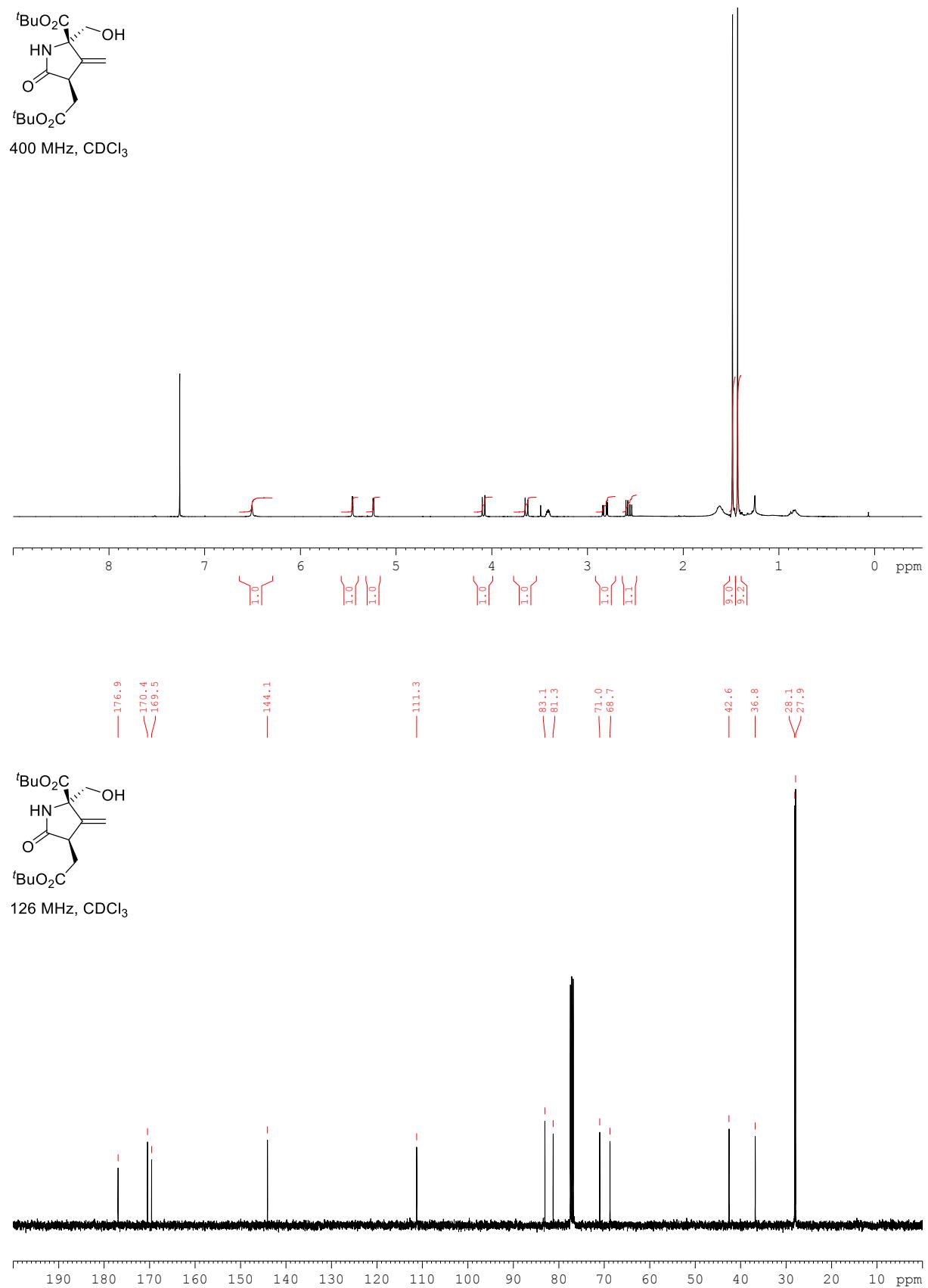
Spectra for compound **39**



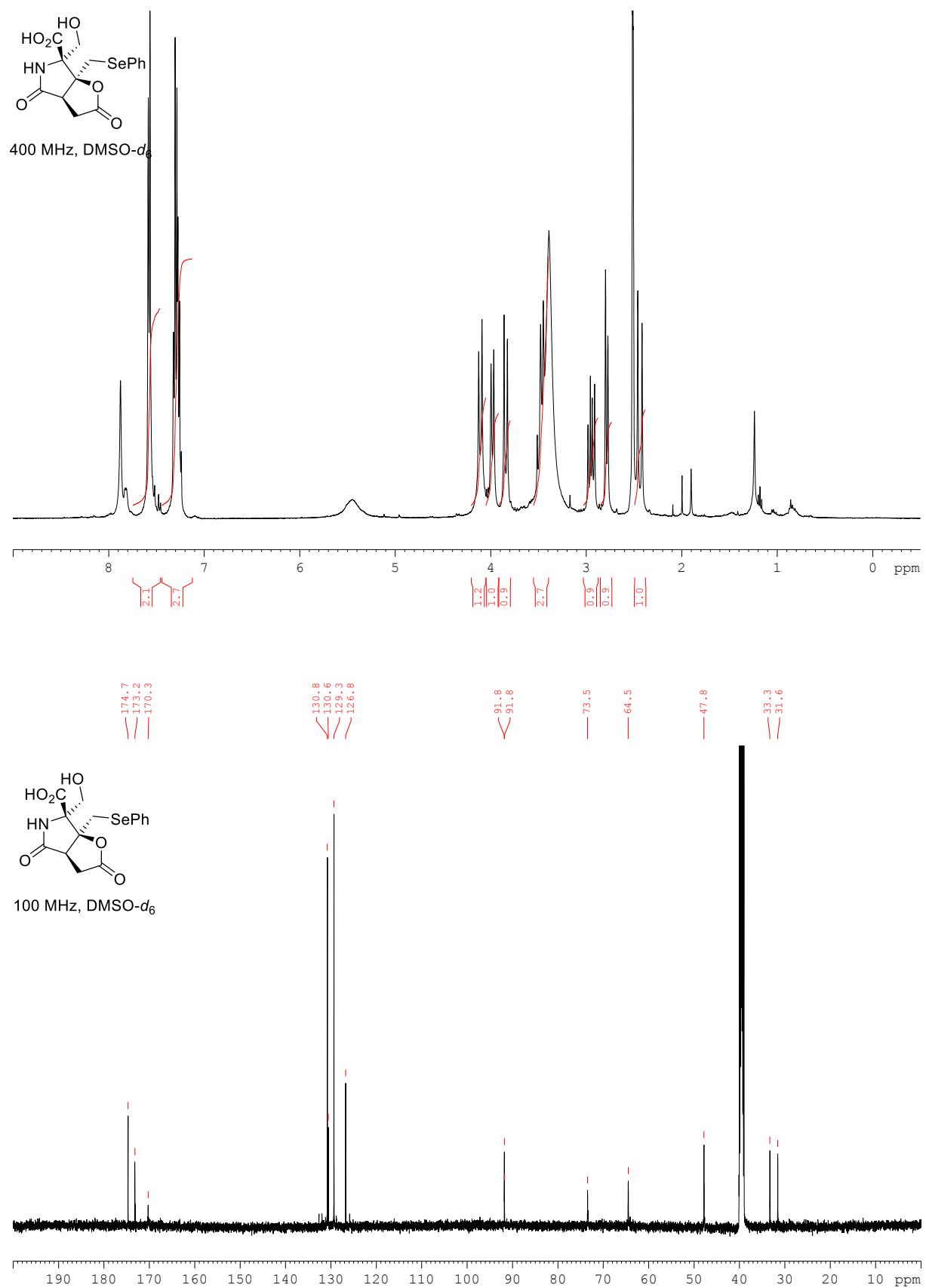
Spectra for compound **40**



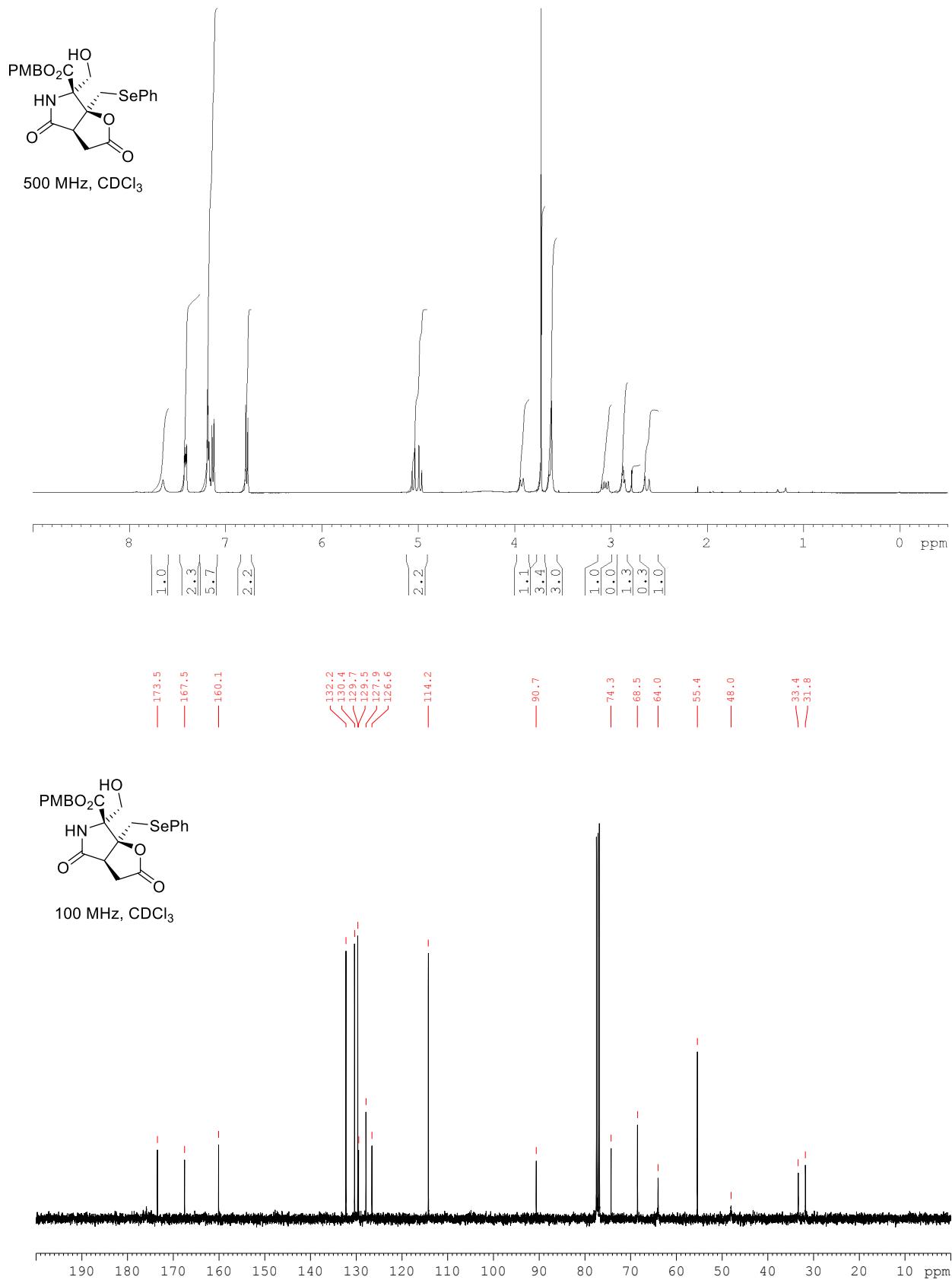
Spectra for compound **41**



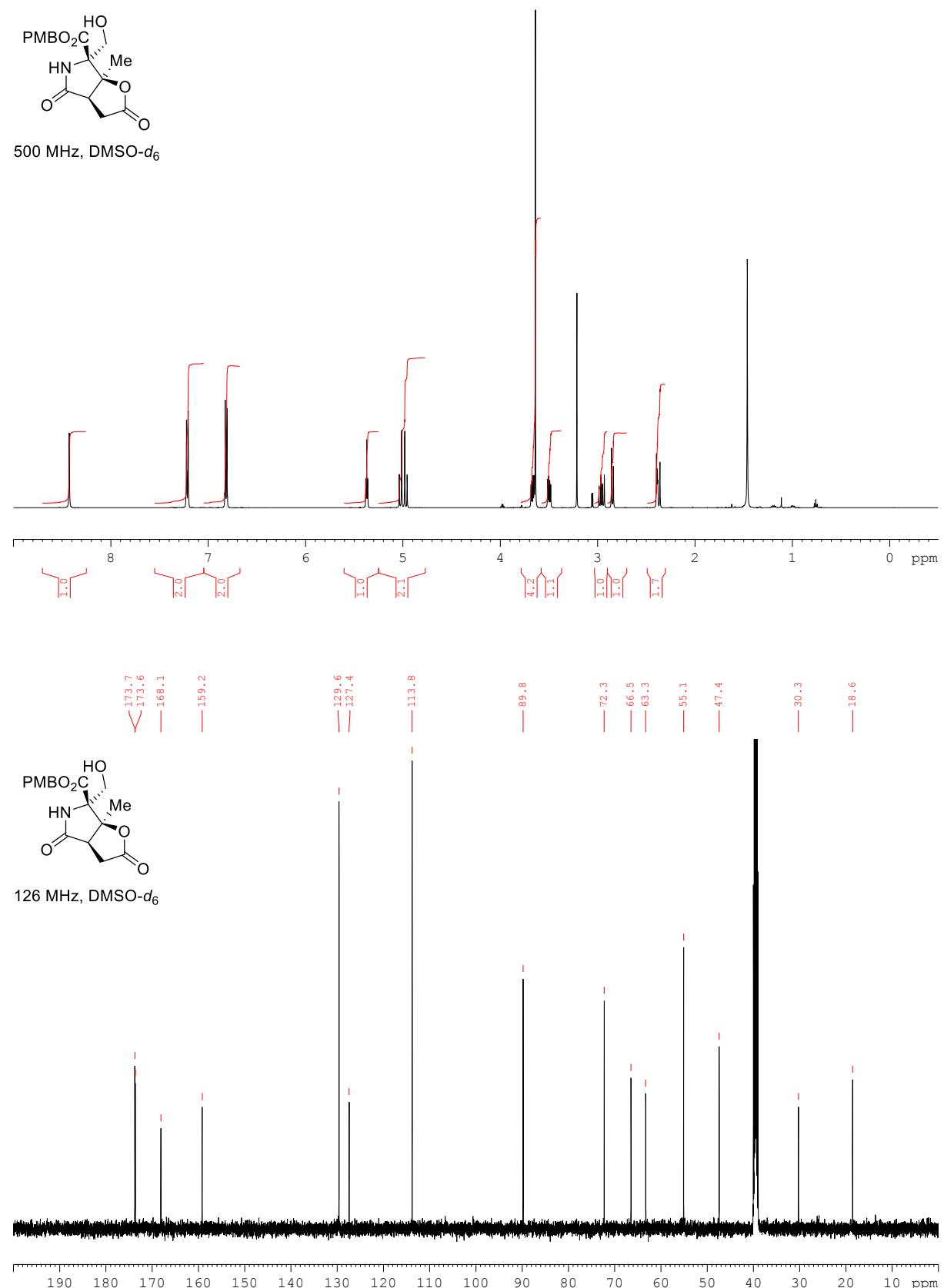
Spectra for compound 42



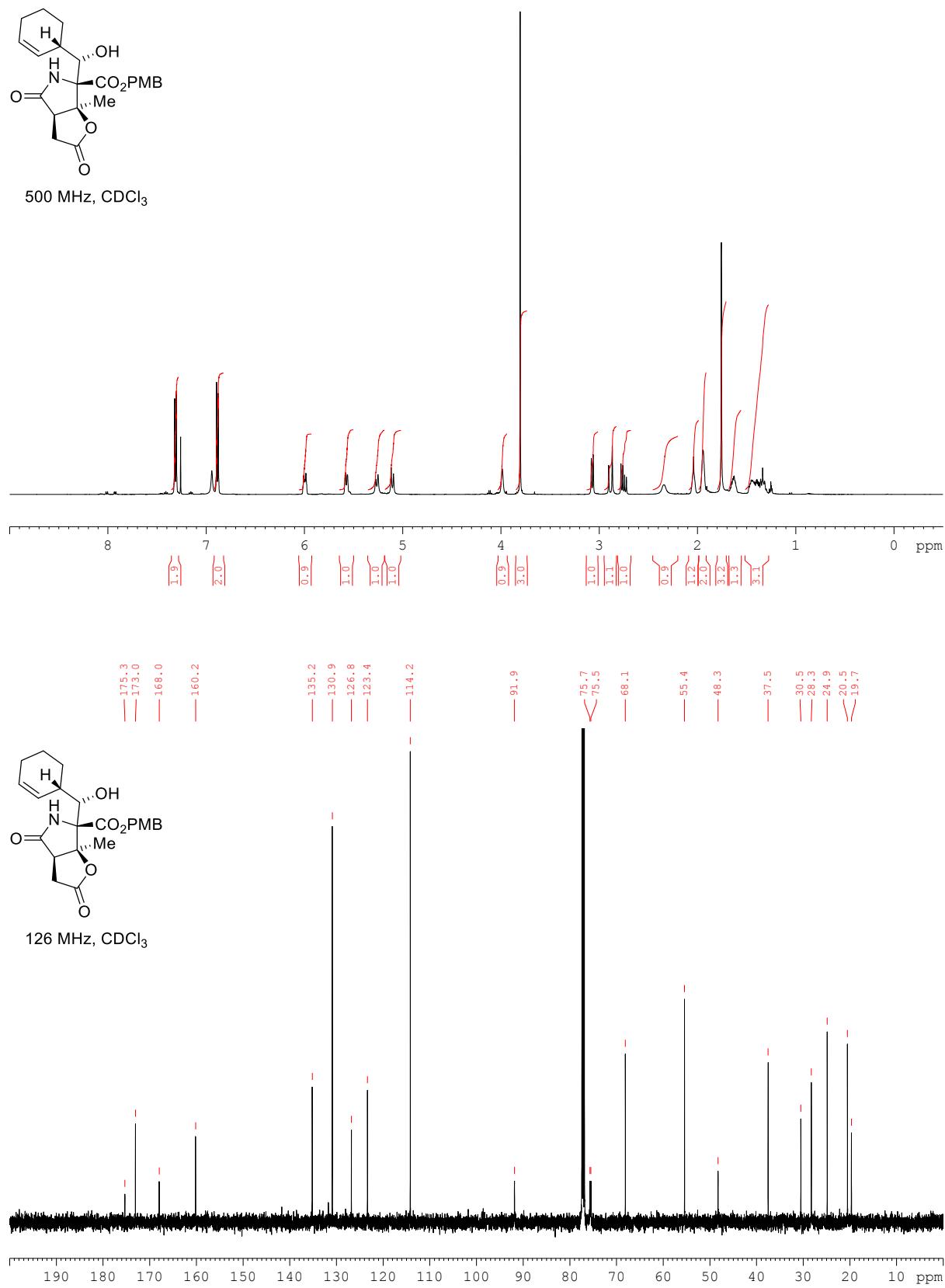
Spectra for compound **43**



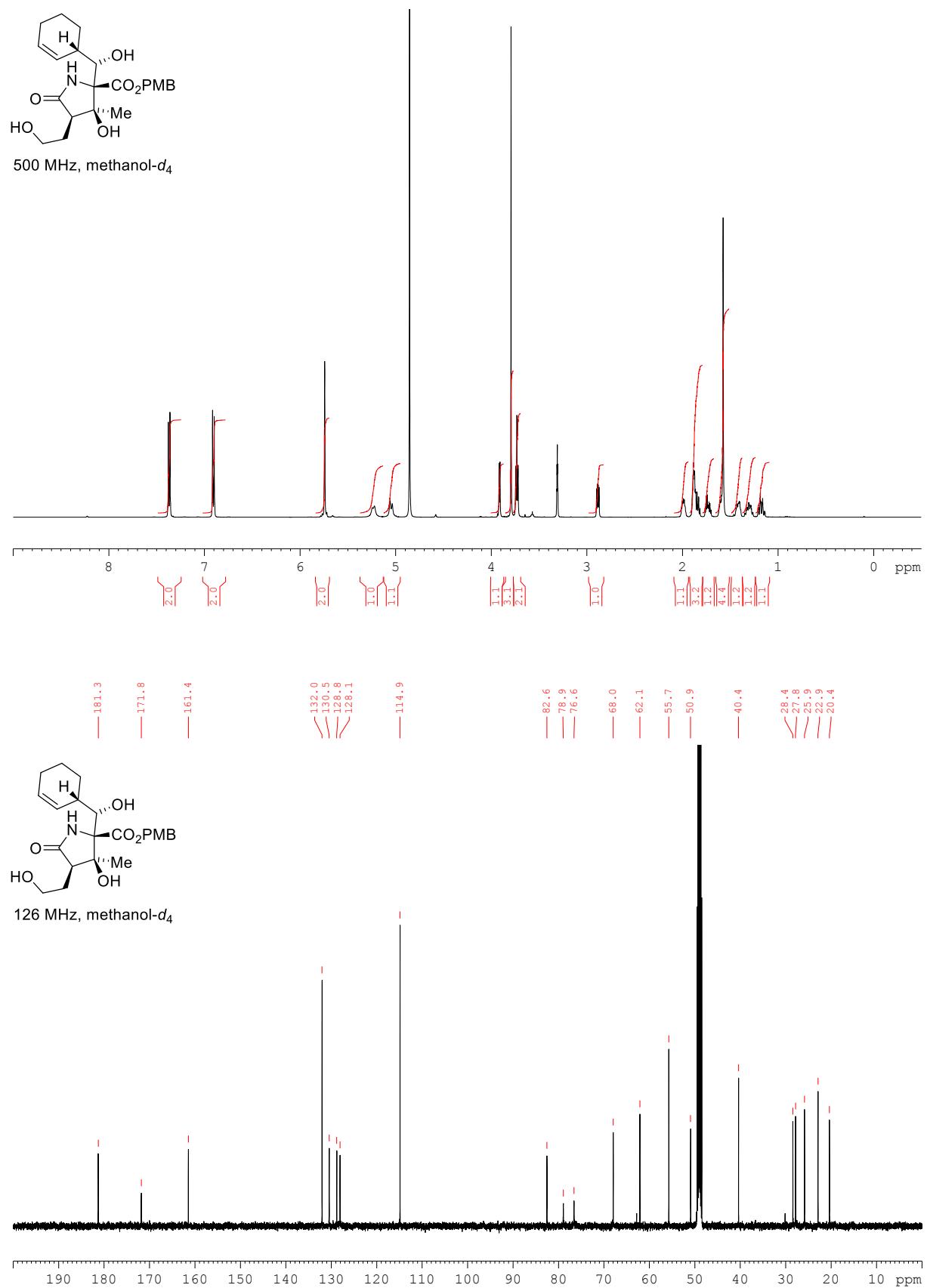
Spectra for compound **44**



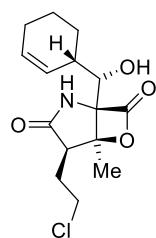
Spectra for compound 47



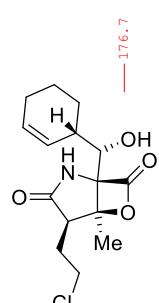
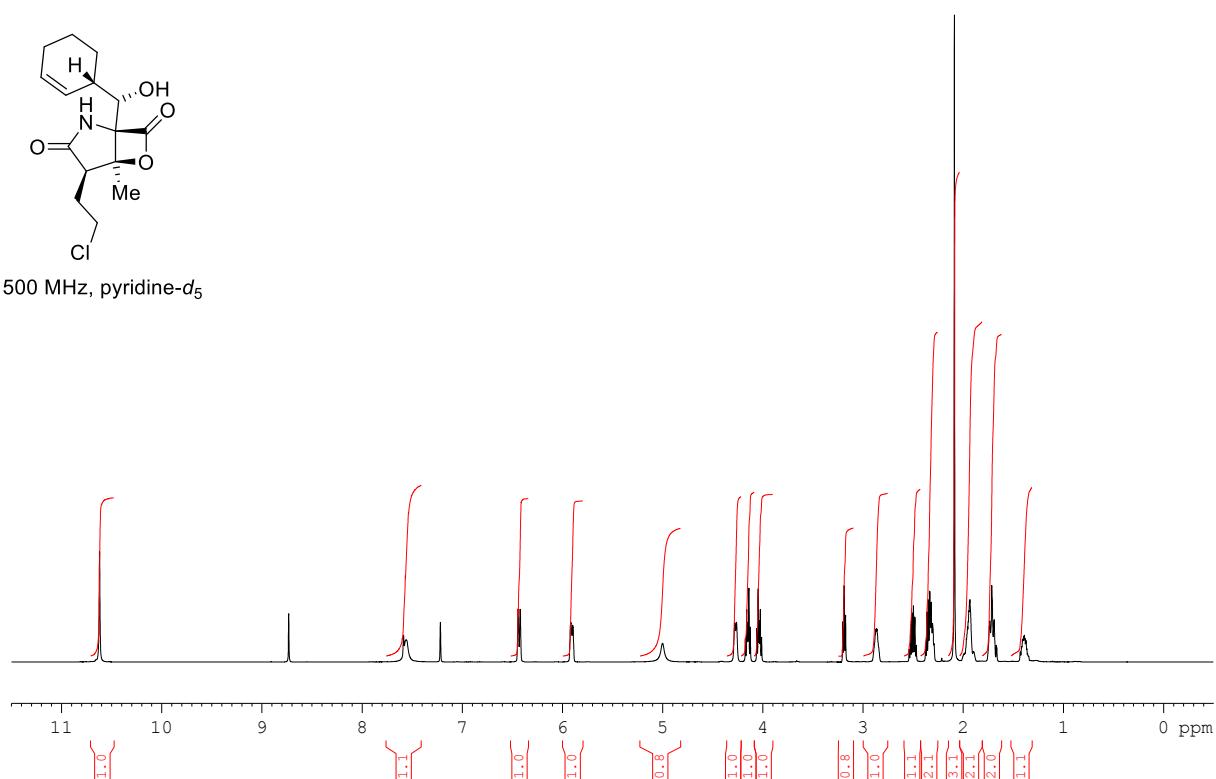
Spectra for compound **48**



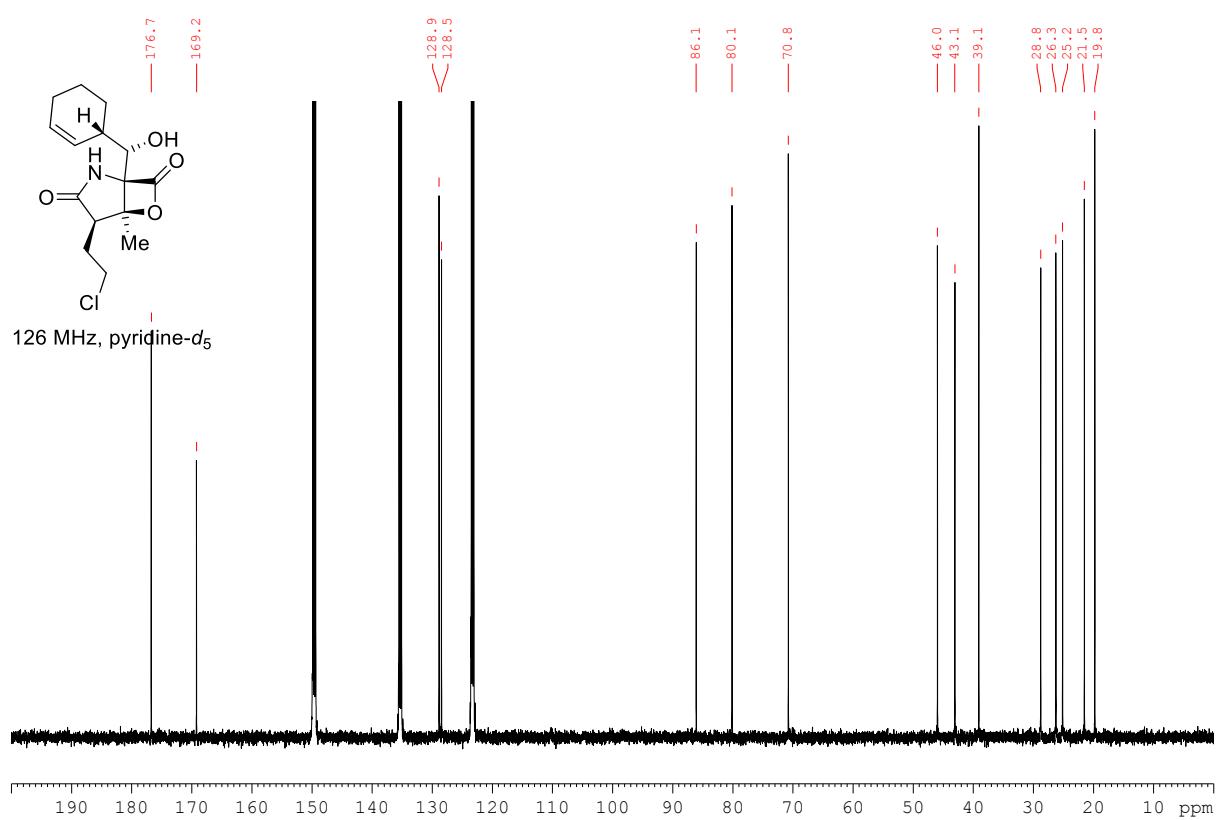
Spectra for salinosporamide A



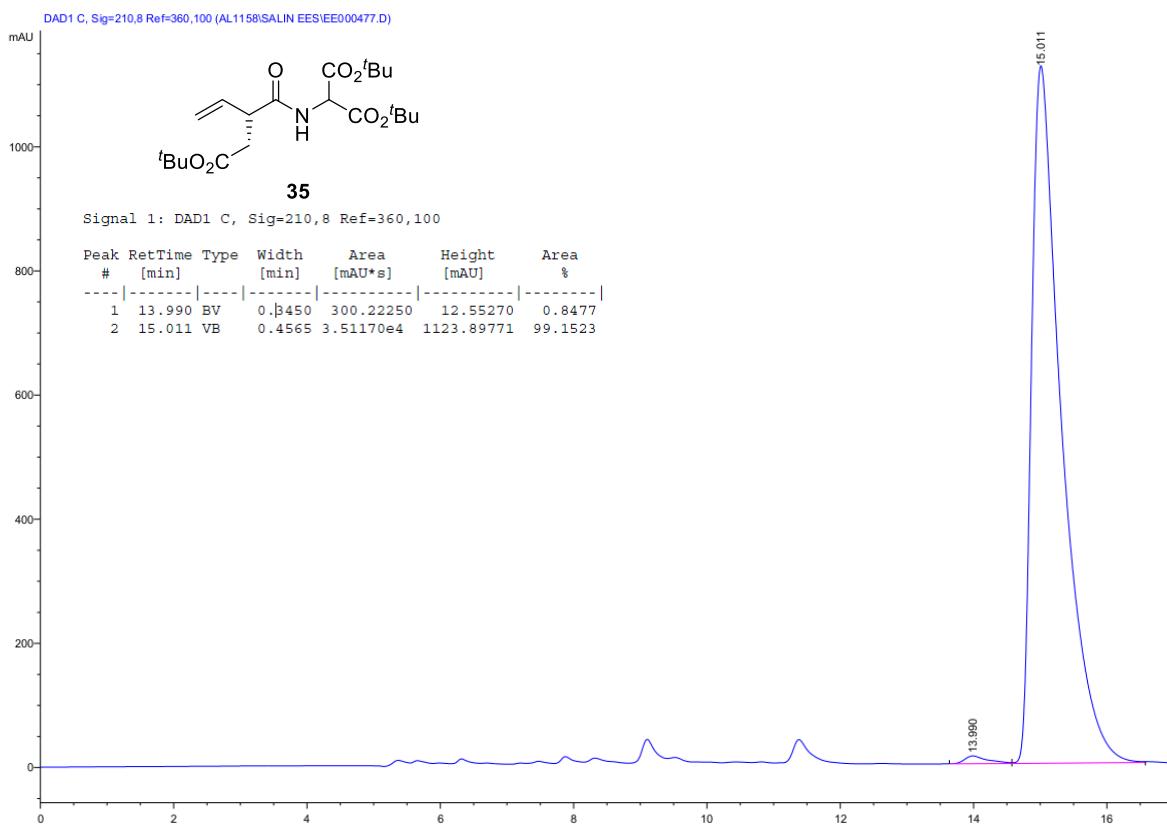
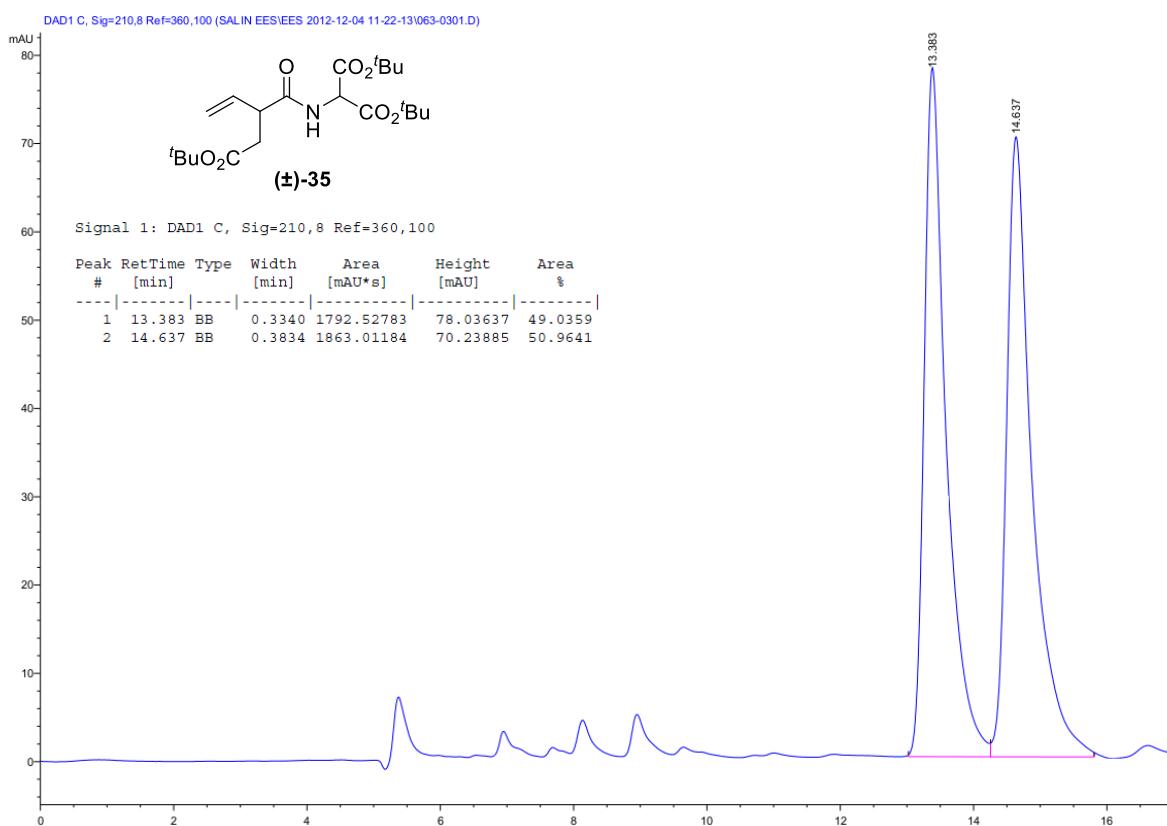
500 MHz, pyridine-*d*₅



126 MHz, pyridine-*d*₅



HPLC traces for compound **35** (ChiralPak AD-H, 10% IPA in hexane, 0.40 mL/min)



HPLC traces for compound **47** (ChiralPak AD-H, 30% IPA in hexane, 0.40 mL/min)

