Diastereoselective Synthesis of Fused Lactone-Pyrrolidinones. Application to a Formal Synthesis (–)-Salinosporamide A

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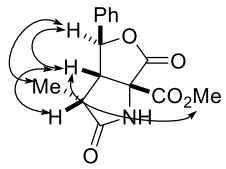
Determination of Stereochemistry

The relative configuration of the [3.3.0]-bicyclic γ-lactones was determined by analysis of 1D nuclear Overhauser effect (nOe) difference or NOESY experiments – see individual compounds for key nOe results. For compounds **12a-c** the relative configuration was assigned by analogy. The relative configuration of the [3.3.0]-bicylcic γ-lactones is in accordance with the Beckwith-Houk model for radical cyclization reactions with substituents placed in the equatorial position of the *pseudo*-chair transition state so as to minimise allylic strain.

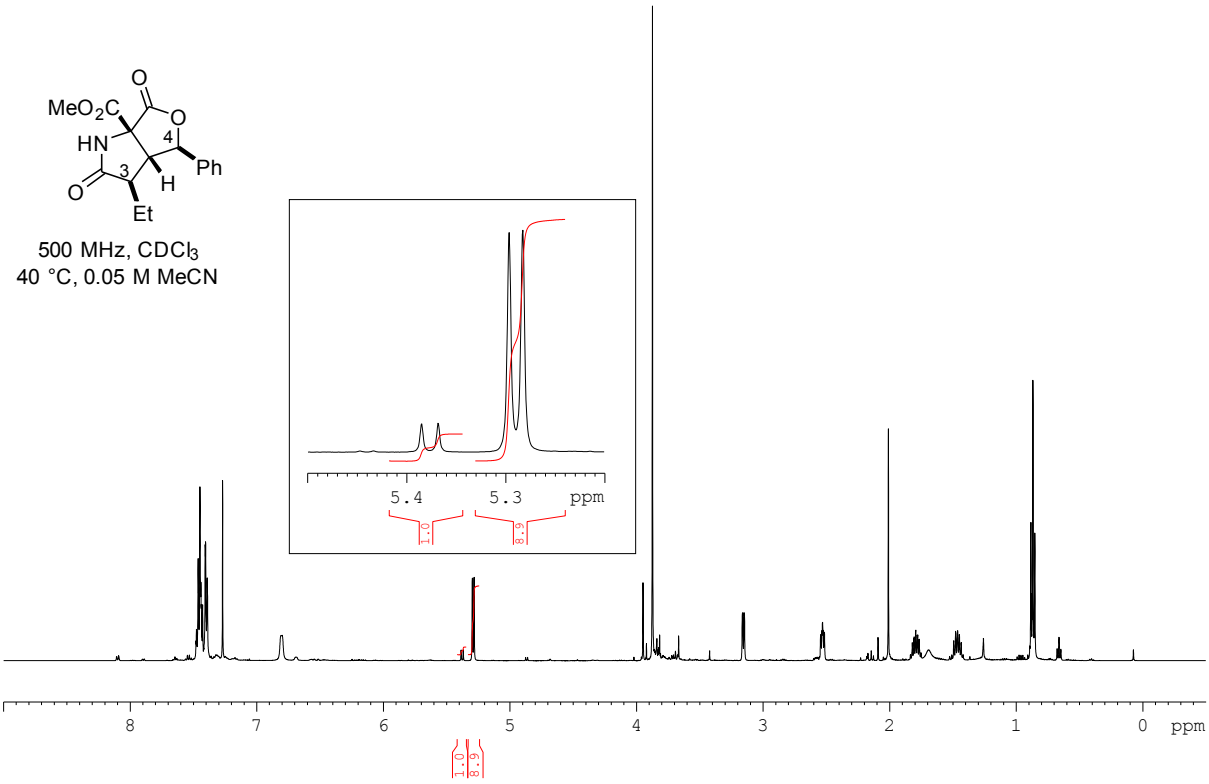
Diastereomeric ratios were determined by analysis of the crude ^{1}H NMR spectra from cyclization where possible.

For the lactones **10**, the benzylic proton of the minor diastereomer, epimeric at C-3, has been observed to be at higher δ_H for all cyclized products, consistent with NOESY spectra of the products (see below). The diastereomers of lactone-pyrrolidinone **10a** were separated by semi-preparative HPLC, and the relative stereochemistry of the minor diastereomer was determined by analysis of the 1D nOe difference spectra. These data showed that the minor diastereomer was the C-3 epimer.



10a minor diastereomer

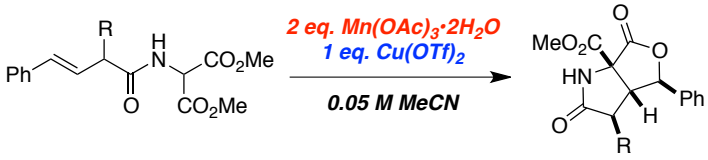
The C-4 epimer was not observed with the lactones **10**. The ethyl (**10b**) substituted cyclized product crude spectrum is shown below as illustration.



Using substrate **7**, the benzylic proton at C-4 in the minor cyclized product **8** was found to be at δ_H 6.06, which is considerably higher than observed for any cyclized product **10**.

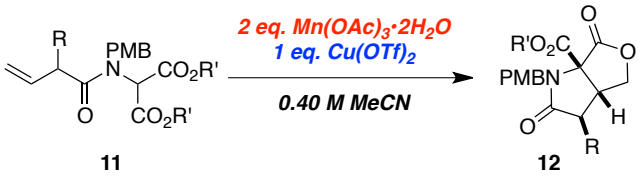
Where possible the ^{13}C and ^{1}H NMR data (or partial data) for the minor diastereomers is listed.

Effect of Temperature on Oxidative Radical Cyclizations



Entry[a]	R	T / °C					
		80		40		25	
		Yield / %	d.r.	Yield / %	d.r.	Yield / %	d.r.
1	H (**7**)	82	5.7:1	73	8.0:1	72	14:1
2	Me (**9a**)	86	4.2:1	76	5.8:1	84	6.6:1
3	Et (**9b**)	68	6.3:1	79	8.7:1	76	11:1
4	^{i}Pr (**9c**)	63	19:1	82	>25:1	81	>25:1
5	^{n}Bu (**9d**)	65	5.0:1	78	8.3:1	65	8.5:1
6	$CH_2C{\equiv}CH$ (**9e**)	95	15:1	75	18:1	76	18:1
7	$CH_2CH{=}CH_2$ (**9f**)	88	9.0:1	76	15:1	74	19:1
8	CH_2Ph (**9g**)	62	5.2:1	84	10:1	87	11:1
9	CH_2CH_2OBn (**9h**)	55	11:1	80	20:1	70	25:1
10[b]	H (**7**)	34	-	trace	-	0	-
11[c]	H (**7**)	20	-	17	-	decomp	-

[a]Diastereomeric ratios were determined from the crude ^{1}H NMR spectra. For R = H, d.r. refers to the mixture of epimers at C-4. For R ≠ H, d.r. refers to the mixture of epimers at C-3. [b]$Mn(OAc)_3{\cdot}2H_2O$ only (2 equivalents); [c]$Cu(OTf)_2$ only (2 equivalents).



11 **12**

Entry[a]	R'	R	T / °C		
			80	40	25
			Yield / %	Yield / %	Yield / %
1	Me	H	62	74	69
2	Et	H	56	48	8
3	^{t}Bu	H	24	75	59
4	^{t}Bu	CH_2Ph	24	52	59
5[b]	^{t}Bu	$CH_2CH{=}CH_2$	40/15	43/26	37/33
6[b,c]	^{t}Bu	$CH_2CH{=}CH_2$	-	65/19	-
7[b,d]	^{t}Bu	$CH_2CH{=}CH_2$	-	10/79	-
8[e]	^{t}Bu	H	40	24	0
9[f]	^{t}Bu	H	decomp	decomp	decomp

[a]The products were isolated in >15:1 dr in all cases; it was not possible to accurately measure the d.r. from the crude ^{1}H NMR spectra; [b]Yield refers to lactone **(+)-12e**/hexahydroindolene **(–)-16**; [c]Two equivalents $Cu(OTf)_2$; [d]0.10 equivalents $Cu(OTf)_2$; [e]$Mn(OAc)_3{\cdot}2H_2O$ only (2 equivalents); [f]$Cu(OTf)_2$ only (2 equivalents).

Experimental Procedures

General Remarks

NMR spectra were recorded on Bruker AV400, DRX500 and AVII500 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. Diasteromeric ratios are measured from crude ^{1}H NMR spectra where possible. Data are quoted for the major diastereomer, which has been separated from the minor diastereomer fully or partially.

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 Daltronics 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 F_{254} 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 CaH_2 and stored over 3 Å molecular sieves. All water used experimentally was distilled. Acetonitrile used for oxidative radical cyclisations were degassed by bubbling dry N_2 through for at least 30 min.

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: *trans*-styrylacetic acid (**S1**),[1] dimethyl 2-aminomalonate hydrochloride (**S2**),[2,3] (*E*)-2-methyl-4-phenylbut-3-enoic acid (**S3**),[4] (*E*)-2-ethyl-4-phenylbut-3-enoic acid (**S4**),[4] (*E*)-2-benzyl-4-phenylbut-

3-enoic acid (**S5**),[4] ((2-iodoethoxy)methyl)benzene (**S6**),[5] 4-(phenylselanyl)butanoic acid (**18**),[6] dimethyl 2-((methoxybenzyl)amino)malonate (**S7**),[7] di-*tert*-butyl bromomalonate (**S8**),[8] 3-benzyldihydrofuran-2(3*H*)-one (**S9**),[9] 3-allyldihydrofuran-2(3*H*)-one (**S10**).[10]

General Procedures

General Procedure A – α-Alkylation of trans-styrylacetic acid S1

According to the procedure of Mermerian and Fu:[11] To a stirred solution of *trans*-styrylacetic acid **S1** (1.00 eq.) in dry THF (0.40 M) at −78 °C was added *n*-butyllithium (1.6 M in hexane 2.20 eq.) dropwise. The mixture was stirred at this temperature for 40 min and the alkyl halide (3.00 eq.) was added dropwise *via* syringe. The reaction mixture was allowed to stir for 16 h with the temperature maintained at −78 °C, and quenched by addition of sat. aq. NH_4Cl solution (20 mL). The mixture was extracted with diethyl ether (3×20 mL) and the combined organic layers washed successively with brine (3×20 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*, which gave the crude alkylated acid.

General Procedure B – Peptide coupling using HBTU

To a stirred solution of the acid (1.0 eq.), dimethyl 2-aminomalonate hydrochloride **S2** (1.1 eq.), diisopropylethylamine (2.0 eq.) in acetonitrile (0.125 M) at room temperature was added HBTU (1.2 eq) in one portion. The reaction was stirred at room temperature until complete by TLC analysis (45–60 min), then quenched with water (25 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed successively with sat. aq. $NaHCO_3$ solution (30 mL), sat. aq. NH_4Cl solution (30 mL), brine (30 mL), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo*, which gave the crude amide.

The crude alylated acid could also be used in the amide coupling reaction without purification, and purified after amidation. The yield for this procedure is also given for each cyclisation substrate.

General Procedure C – Cyclization of aryl substrates to give fused γ-lactone-pyrrolidinones

To a degassed mixture of amidomalonate (0.300 mmol, 1.00 eq.), manganese(III) acetate dihydrate (0.600 mmol, 2.00 eq.), and copper(II) triflate (0.300 mmol, 1.00 eq.) was added N_2 sparged acetonitrile (0.05 M). The mixture was stirred at 25 °C for 4 h and then quenched by addition of water (15 mL). The aqueous layer was extracted with chloroform (3×15 mL), and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo*, which gave the crude fused lactone-pyrrolidinone.

General Procedure D – Preparation of N-PMB amidomalonates

According to the procedure of Hatakeyema et al.:[7] To a stirred solution of carboxylic acid (1.00 eq.) in DCM (1.0 M) with DMF (0.10 eq.) was added oxalyl chloride (1.10 eq.) dropwise (*caution, gas evolution!*). After 1 h, this solution was added rapidly to a **vigorously** stirred mixture of di-*tert*-butyl 2-((4-methoxybenzyl)amino)malonate **22** (1.10 eq.) in DCM (1.40 mL/mmol) and sat. aq. $NaHCO_3$ (0.90 mL/mmol). When the reaction was judged complete by TLC analysis (30–60 min) the layres were separated and the oganic layer was filtered through a silica pad eluting with diethyl ether. The solvent was removed *in vacuo*, which gave the crude amidomalonate.

General Procedure E – Terminal alkene formation through oxidation and elimination of phenylselanol

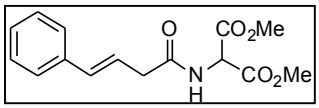
According to the modified procedure of Hoornaert et al.:[12] To a stirred solution of *N*-PMB amidomalonate (1.00 eq) in DCM (0.020 M) at –15 °C was added *m*-CPBA (70–75% with water, 3.00 eq.) in DCM (5.8 mL/mmol *m*-CPBA). The solution was allowed to warm to room temperature and stirred for 30 min. Dimethyl sulfide (2.0 eq.) and diisopropylamine (6.0 eq.) were added and the reaction was heated under reflux until it was judged complete by TLC analysis (5–6 h). The solvent was removed *in vacuo*, which gave the crude terminal alkene.

General Procedure F – Cyclization of terminal alkenes to give fused γ-lactone pyrrolidinones

To a degassed mixture of the terminal alkene (1.00 eq.), manganese(III) acetate dihydrate (2.00 eq.) and copper(II) triflate (1.00 eq.) was rapidly added nitrogen sparged MeCN (0.40 M). The reaction mixture was heated at 40 °C for 4 h, cooled to RT and quenched by the addition of water (10 mL). The organic layer was extracted with chloroform (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and the solvent was removed *in vacuo*, which gave the crude pyrrolidinone-lactones.

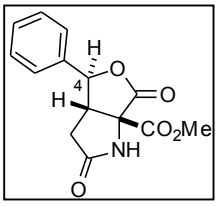
Synthesis and Spectroscopic Data

(E)-Dimethyl 2-(4-phenylbut-3-enamido)malonate **7**



Prepared from *trans*-styrylacetic acid **S1** (1.50 g, 9.24 mmol) using General Procedure B and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), then by recrystallization (dichloromethane/hexane), which gave *(*E*)-dimethyl 2-(4-phenylbut-3-enamido)malonate* **7** as a white crystalline solid (1.64 g, 5.63 mmol, 61%); *m.p.* 101–102 °C; R_f = 0.28 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3299w (N–H), 2927w (C–H), 1746s (C=O ester), 1648m (C=O amide); δ_H (400 MHz, $CDCl_3$) 3.26 (2H, dd, *J* = 7.2, 1.4, CH_2C(O)), 3.83 (6H, s, CO_2CH_3), 5.23 (1H, d, *J* = 7.0, NHC*H*), 6.31 (1H, dt, *J* = 15.8, 7.2, PhCH=C*H*), 6.60 (1H, d, *J* = 15.8, PhC*H*=CH), 6.71 (1H, d, *J* = 6.5, N*H*), 7.23–7.26 (1H, m, Ar*H*), 7.31 (2H, t, *J* = 7.5, Ar*H*), 7.40 (2H, d, *J* = 7.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.1 (*C*H_2), 53.6 (*C*H_3), 56.2 (*C*H), 121.5 (*C*H), 126.5 (*C*H), 127.9 (*C*H) 128.7 (*C*H), 135.1 (*C*H), 136.6 (*C*), 166.8 (*C*(O)), 170.7 (*C*(O)); *m/z* LRMS (ESI+) 314 ($M+Na^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 314.0999; $[C_{15}H_{17}NNaO_5]^+$ requires 314.0999.

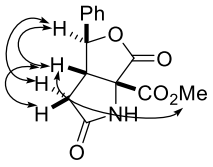
(3aS,4S*,6aS*)-Methyl 2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **8**



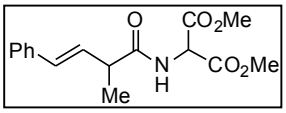
Formed as a 6:1 mixture of C-4 epimers from (*E*)-dimethyl 2-(4-phenylbut-3-enamido)malonate **7** (87.3 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (20:1 chloroform:methanol), which gave *methyl 2,6-dioxo-4-phenylhexahydro-1H-furo[3,4-*b*]pyrrole-6*a*-carboxylate* **8** as a white crystalline solid (59.4 mg, 0.216 mmol, 72%); *m.p.* 169–173 °C; R_f = 0.17 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2916m (N–H), 1775s (C=O γ-lactone), 1724s (C=O ester), 1696s (C=O γ-lactam); δ_H (500 MHz, $CDCl_3$) 2.49 (1H, dd, *J* = 17.8, 1.5, C*H*H'C(O)), 2.72 (1H, dd, *J* = 17.8, 8.6, CH*H*'C(O)), 3.43 (1H, ddd, *J* = 8.6, 7.5, 1.5, PhCHC*H*CH_2), 3.87 (3H, s, CO_2CH_3), 5.20 (1H, d, *J* = 7.5, PhC*H*), 6.67 (1H, br s, N*H*), 7.40 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 34.3 (*C*H_2), 48.2 (*C*H), 54.2 (*C*H_3), 69.4 (*C*), 86.4 (*C*H), 126.1 (*C*H), 129.4 (*C*H), 129.8 (*C*H), 136.7 (*C*),

168.3 (*C*(O)), 169.7 (*C*(O)), 174.5 (*C*(O)); *m/z* LRMS (ESI+) 298 ($M+Na^+$, 38%), 339 ($M+MeCN+Na^+$, 100), 573 ($2M+Na^+$, 70); HRMS (ESI+) found $[M+Na]^+$ 298.0680; $[C_{14}H_{13}NNaO_5]^+$ requires 298.0686. *For the minor diastereomer, the characteristic δ_H of the benzylic proton was found at 6.06 (1H, d, J = 6.7), but it was not possible to resolve other resonances or isolate the minor diastereomer.*

Key nOe data:

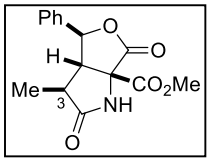


(E)-Dimethyl 2-(2-methyl-4-phenylbut-3-enamido)malonate 9a



Prepared from (*E*)-2-methyl-4-phenylbut-3-enoic acid **S3** (176 mg, 1.00 mmol) using General Procedure B but with free amine dimethyl aminomalonate (162 mg, 1.10 mmol) rather than the hydrochloride salt and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(E)-dimethyl 2-(2-methyl-4-phenylbut-3-enamido)malonate* **9a** as a colourless oil (92.0 mg, 0.300 mmol, 30%); R_f = 0.27 (1:1 petroleum ether 40–60 °C:ethyl acetate); *m.p.* 85–86 °C; ν_{max} (thin film) 3302m (N−H), 2956m (C−H), 1761s (C=O malonate), 1747s (C=O malonate), 1665s (C=O amide I), 1511s (C=O amide II); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* = 7.0, CH=CHCH*C*H_3), 3.26 (1H, ddq, *J* = 7.9, 1.0, 7.0, CH=CHC*H*Me), 3.81 (3H, s, CO_2C*H*$_3$), 3.83 (3H, s, CO_2C*H*$_3$), 5.20 (1H, d, *J* = 6.9, C*H*NH), 6.27 (1H, dd, *J* = 7.9, 15.9, CH=C*H*CHMe), 6.59 (1H, d, *J* = 15.9, C*H*=CHCHMe), 6.63 (1H, d, *J* = 6.9, CHN*H*), 7.22–7.42 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 17.4 (*C*H_3), 44.3 (*C*H), 53.5 (*C*H_3), 56.2 (*C*H), 126.4 (*C*H), 127.8 (*C*H), 128.6 (*C*H), 128.8 (*C*H), 132.4 (*C*H), 136.7 (*C*), 166.7 (*C*(O)), 166.8 (*C*(O)), 173.8 (*C*(O)); *m/z* LRMS (ESI+) 306 ($M+H^+$, 100%), 328 ($M+Na^+$, 37); HRMS (ESI+) found $[M+Na]^+$ 328.1146; $[C_{16}H_{19}NNaO_5]^+$ requires 328.1155. *Yield over two steps from carboxylic acid* **S1**: 1.22 g, 4.00 mmol, 65%.

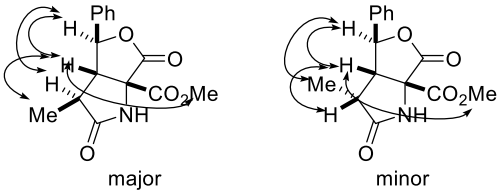
(3S,3aS*,4S*,6aS*)-Methyl 3-methyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylateI* 10a

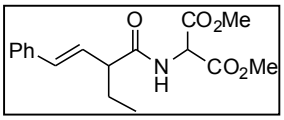


Formed as a 6.6:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-methyl-4-phenylbut-3-enamido)malonate **9a** (91.5 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3aS*,4S*,6aS*)-methyl 3-methyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10a** as a white solid (72.8 mg, 0.252 mmol, 84%); R_f = 0.15 (1:1 petroleum ether 40–60 °C:ethyl acetate). The diastereomers were separated by semi-preparative HPLC (10% IPA in hexane), which gave the major diastereomer as colourless crystals; *m.p.* 104–107 °C (10% IPA in hexane); HPLC t_r = 18 min; ν_{max} (thin film) 3225 brm (N−H), 2959m (C−H), 1782s (C=O *γ*-lactone), 1758s (C=O ester), 1716s (C=O *γ*-lactam); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* = 7.6, *H*$_3$CCHC(O)), 2.65 (1H, dq, *J* = 1.9, 7.6, MeC*H*C(O)), 3.11 (1H, dd, *J* = 7.0, 1.9, PhCHC*H*), 3.87 (3H, s, CO_2C*H*$_3$), 5.29 (1H, d, *J* = 7.0, PhC*H*), 6.48 (1H, br s, N*H*), 7.33–7.46 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 17.1 (*C*H_3), 41.6 (*C*H), 54.1 (*C*H_3), 56.0 (*C*H), 68.2 (*C*), 85.7 (*C*H), 125.9 (*C*H), 129.4 (*C*H), 129.7 (*C*H), 137.1 (*C*), 168.7 (*C*(O)), 169.9 (*C*(O)), 177.7 (*C*(O)); *m/z* LRMS (ESI+) 312 ($M+Na^+$, 65%), 601 ($2M+Na^+$, 100); HRMS (ESI+) found $[M+Na]^+$ 312.0840; $[C_{15}H_{15}NNaO_5]^+$ requires 312.0842. Further elution gave the minor diastereomer as colourless needle-like crystals; *m.p.* 186—190 °C (10% IPA in hexane); HPLC t_r = 22 min; ν_{max} (thin film) 3244 brm (N−H), 2942m (C−H), 1781s

(C=O γ-lactone), 1757s (C=O ester), 1717s (C=O lactam); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* = 7.5, H_3CCHC(O)), 2.83 (1H, dd, *J* = 7.5, 7.5, MeC*H*C(O)), 3.64 (1H, dd, *J* = 8.0, 7.5, PhCHC*H*), 3.93 (3H, s, CO_2CH_3), 5.43 (1H, d, *J* = 8.0, PhC*H*), 6.44 (1H, br s, N*H*), 7.40—7.50 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 10.5 (*C*H_3), 37.7 (C*H*), 52.0 (PhCH*C*H), 54.2 (*C*H_3), 67.9 (*C*), 81.6 (*C*H), 127.3 (*C*H), 129.3 (*C*H), 129.9 (*C*H), 136.9 (*C*), 168.3 (*C*(O)), 169.5 (*C*(O)), 176.6 (*C*(O)); *m/z* LRMS (ESI+) 312 ($M+Na^+$, 100%), 601 ($2M+Na^+$, 30); HRMS (ESI+) found $[M+H]^+$ 290.1016; $[C_{15}H_{16}NO_5]^+$ requires 290.1023.

Key nOe data:

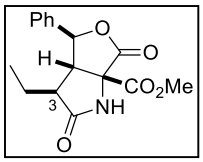




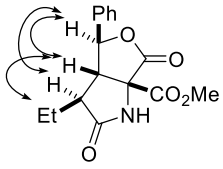
*(*E*)-Dimethyl 2-(2-ethyl-4-phenylbut-3-enamido)malonate* **9b**

Prepared from (*E*)-2-ethyl-4-phenylbut-3-enoic acid **S4** (100 mg, 0.526 mmol) and dimethyl aminomalonate hydrochloride **S2** (106 mg, 0.578 mmol) using General Procedure B and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-methyl-4-phenylbut-3-enamido)malonate* **9b** as a white solid (108 mg, 0.338 mmol, 64%); *m.p.* 104–105 °C; R_f = 0.25 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3315m (N−H), 2960m (C−H), 1760s (C=O malonate), 1748s (C=O malonate), 1653s (C=O amide I), 1537s (C=O amide II); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* = 7.6, CH_3), 1.65 (1H, ddq, *J* = 6.0, 13.5, 7.6, H_3CC*H*H'), 1.93 (1H, ddq, *J* = 7.3, 13.5, 7.6, H_3CCH*H*'), 2.97 (1H, ddd, *J* = 8.9, 7.3, 6.0, C*H*C(O)), 3.78 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 5.18 (1H, d, *J* = 6.8, C*H*$(CO_2Me)_2$), 6.19 (1H, dd, *J* = 8.9, 15.9, PhCH=C*H*), 6.52 (1H, d, *J* = 15.9, PhC*H*=CH), 6.59 (1H, d, *J* = 6.8, N*H*), 7.12–7.45 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.8 (*C*H_3), 25.7 (*C*H_2), 52.4 (*C*H), 53.6 (CH_3), 53.6 (*C*H_3), 56.3 (*C*H), 126.5 (*C*H), 127.7 (*C*H), 127.8 (*C*H), 128.7 (*C*H), 133.3 (*C*H), 136.8 (*C*), 166.8 (*C*(O)), 166.9 (*C*(O)), 173.4 (*C*(O)); *m/z* LRMS (ESI+) 320 ($M+H^+$, 52%), 342 ($M+Na^+$, 30), 656 ($2M+NH_4^+$, 63), 661 ($2M+Na^+$, 100); HRMS (ESI+) found $[M+Na]^+$ 342.1312; $[C_{17}H_{21}NNaO_5]^+$ requires 342.1312. *Yield over two steps from carboxylic acid* **S1**: 280 mg, 0.878 mmol, 14%.

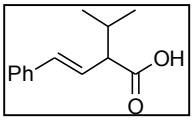
(3S,3aS*,4S*,6aS*)-Methyl 3-ethyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10b**



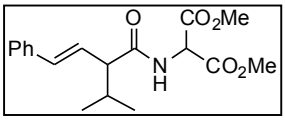
Formed as an 11:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-ethyl-4-phenylbut-3-enamido)malonate **9b** (95.7 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3a*S**,4S*,6a*S**)-methyl 3-ethyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10b** as a white solid (69.1 mg, 0.228 mmol, 76%), characterisation is on the mixture; *m.p.* 139–141 °C; R_f = 0.12 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3226 brm (N−H), 2964m (C−H), 1782s (C=O γ-lactone), 1759s (C=O ester), 1714s (C=O γ-lactam); δ_H (500 MHz, $CDCl_3$) 0.86 (3H, t, *J* = 7.4, H_3CCH_2), 1.37–1.55 (1H, m, H_3CC*H*H'), 1.71–1.88 (1H, m, H_3CCH*H*'), 2.53 (1H, ddd, *J* = 8.5, 5.4, 1.9, C*H*C(O)), 3.15 (1H, dd, *J* = 6.9, 1.9, PhCHC*H*), 3.87 (3H, s, CO_2CH_3), 5.29 (1H, d, *J* = 6.9, PhC*H*), 6.95 (1H, br s, N*H*), 7.36–7.50 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 11.5 (*C*H_3), 24.5 (*C*H_2), 48.8 (*C*H), 53.6 (*C*H_3), 54.1 (*C*H), 68.6 (*C*), 86.2 (*C*H), 125.8 (*C*H), 129.3 (*C*H), 129.6 (*C*H), 137.1 (*C*), 168.8 (*C*(O)), 170.2 (*C*(O)), 177.3 (*C*(O)); *m/z* (ESI+) found $[M+Na]^+$ 326.0998; $[C_{16}H_{17}NNaO_5]^+$ requires 326.0999;

Key nOe data: 

*(*E*)-2-Isopropyl-4-phenylbut-3-enoic acid* S11



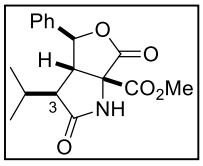
Prepared from *trans*-styrylacetic acid **S1** (1.00 g, 6.17 mmol) and isopropyl bromide (3.15 g, 18.51 mmol) using General Procedure A and purified by flash column chromatography (3:1 petroleum ether 40–60 °C:ethyl acetate), then recrystallization (dichloromethane/isohexane), which gave *(*E*)-2-isopropyl-4-phenylbut-3-enoic acid* **S11** as a white crystalline solid (275 mg, 1.35 mmol, 22%); *m.p.* 80–81 °C; R_f = 0.15 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3107br (O-H), 2969m (C−H), 1699s (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* = 6.8, CH(C*H*$_3$)(CH$_3$)), 1.01 (3H, d, *J* = 6.8, CH(CH$_3$)(C*H*$_3$)), 2.08–2.20 (1H, m, C*H*Me$_2$), 2.73–2.96 (1H, dd, *J* = 8.7, 9.5, PhCH=CHC*H*), 6.17 (1H, dd, *J* = 9.5, 15.9, PhCH=C*H*), 6.47 (1H, d, *J* = 15.9, PhC*H*=CH), 7.12–7.47 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 19.9 (*C*H$_3$), 21.0 (*C*H$_3$), 31.3 (*C*H), 57.2 (*C*H), 126.1 (*C*H), 126.5 (*C*H), 127.8 (*C*H), 128.7 (*C*H), 133.8 (*C*H), 136.9 (*C*), 179.3 (*C*(O)); *m/z* LRMS (ESI−) 159 (M-CO_2H^-, 46%), 203 (M-H^-, 28); HRMS (ESI+) found $[M+Na]^+$ 227.1039; $[C_{13}H_{16}NaO_2]^+$ requires 227.1043.



*(*E*)-Dimethyl 2-(2-isopropyl-4-phenylbut-3-enamido)malonate* 9c

Prepared from (*E*)-2-isopropyl-4-phenylbut-3-enoic acid **S11** (100 mg, 0.490 mmol) and dimethyl aminomalonate hydrochloride **S2** (99 mg, 0.539 mmol) using General Procedure C and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-isopropyl-4-phenylbut-3-enamido)malonate* **9c** as a white solid (108 mg, 0.338 mmol, 64%); *m.p.* 86–87 °C; R_f = 0.20 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3302m (N−H), 2958m (C−H), 1767s (C=O malonate), 1746 (C=O malonate), 1656s (C=O amide I), 1526s (C=O amide II); δ_H (500 MHz, $CDCl_3$) 0.96 (3H, d, *J* = 6.8, CH(C*H*$_3$)(CH$_3$)), 1.01 (3H, d, *J* = 6.8, CH(CH$_3$)(C*H*$_3$)), 2.08–2.30 (1H, m, C*H*Me$_2$), 2.76 (1H, dd, *J* = 9.1, 8.3, PhCH=CHC*H*), 3.81 (3H, s, CO_2CH_3), 3.82 (3H, s, CO_2CH_3), 5.20 (1H, d, *J* = 6.6, C*H*NH), 6.24 (1H, dd, *J* = 15.9, 9.1, PhCH=C*H*), 6.51 (1H, d, *J* = 15.9, PhC*H*=CH), 6.59 (1H, br d, *J* = 6.6, N*H*), 7.21–7.42 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 19.9 (*C*H$_3$), 21.0 (*C*H$_3$), 31.0 (*C*H), 53.5 (*C*H$_3$), 53.6 (*C*H$_3$), 56.3 (*C*H), 58.6 (*C*H), 126.5 (*C*H), 126.6 (*C*H), 127.8 (*C*H), 128.7 (*C*H), 133.8 (*C*H), 136.9 (*C*), 166.8 (*C*(O)), 166.9 (*C*(O)), 173.3 (*C*(O)); *m/z* LRMS (ESI+) 334 (M+H^+, 42%), 689 (2M+Na^+, 100); HRMS (ESI+) found $[M+Na]^+$ 356.1478; $[C_{18}H_{23}NNaO_5]^+$ requires 356.1468. *Yield over two steps from carboxylic acid* **S1**: 310 mg, 0.931 mmol, 15%.

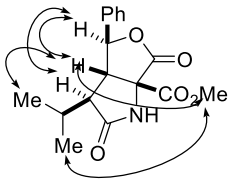
(3S,3aS*,4S*,6aS*)-Methyl 3-isopropyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* 10c



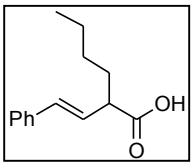
Formed as a >25:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-isopropyl-4-phenylbut-3-enamido)malonate **9c** (100 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3*aS**,4S*,6*aS**)-methyl 3-isopropyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a-carboxylate* **10c** as a white

solid (77.0 mg, 0.243 mmol, 81%); *m.p.* 148–149 °C; R_f = 0.16 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 1782s (C=O *γ*-lactone), 1760s (C=O ester), 1710s (C=O *γ*-lactam); δ_H (500 MHz, $CDCl_3$) major diastereomer: 0.69 (3H, d, *J* = 6.8, (H_3C)(H$_3$C)CH), 0.78 (3H, d, *J* = 6.9, (H$_3$C)(H_3C)CH), 2.12–2.21 (1H, m, (H$_3$C)$_2$C*H*), 2.54 (1H, dd, *J* = 2.2, 4.4, *i*PrC*H*C(O)), 3.16 (1H, dd, *J* = 2.2, 6.5, PhCHC*H*), 3.84 (3H, s, CO_2CH_3), 5.24 (1H, d, *J* = 6.5, PhC*H*), 6.95 (1H, br s, N*H*), 7.33–7.49 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 18.0 (*C*H$_3$), 20.7 (*C*H$_3$), 28.7 (*C*H), 50.2 (*C*H), 54.1 (*C*H$_3$), 54.4 (*C*H), 68.9 (*C*), 87.4 (*C*H), 125.9 (*C*H), 129.3 (*C*H), 129.6 (*C*H), 137.2 (*C*), 168.7 (*C*(O)), 170.5 (*C*(O)), 176.8 (*C*(O)); *m/z* LRMS (ESI−) 316 (M-H$^-$, 100%); HRMS (ESI+) found [M+Na]$^+$ 340.1159; [$C_{17}H_{19}NNaO_5$]$^+$ requires 340.1155.

Key nOe data:

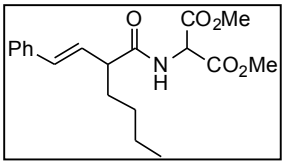


*(*E*)-2-Butyl-4-phenylbut-3-enoic acid* S12



Prepared from *trans*-styrylacetic acid **S1** (1.00 g, 6.17 mmol) and *n*-butyl bromide (2.02 g, 18.5 mmol) using General Procedure A and purified by flash column chromatography (3:1 petroleum ether 40–60 °C:ethyl acetate), then recrystallization (dichloromethane/isohexane), which gave *(*E*)-2-butyl-4-phenylbut-3-enoic acid* **S12** as a white crystalline solid (461 mg, 2.11 mmol, 34%); *m.p.* 46–50 °C; R_f = 0.18 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3317br (O-H), 2929m (C−H), 1705s (C=O carboxylic acid); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* = 7.0, C*H*$_3$), 1.26–1.45 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 1.55–1.87 (1H, m, *n*PrC*H*H'), 1.76–2.02 (1H, m, nPrCH*H*'), 3.19 (1H, ddd, *J* = 7.4, 7.4, 8.8, C*H*CO$_2$H), 6.20 (1H, dd, *J* = 15.9, 8.8, PhCH=C*H*), 6.51 (1H, d, *J* = 15.9, PhC*H*=CH), 7.08–7.58 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 22.6 (*C*H$_2$), 29.4 (*C*H$_2$), 32.4 (*C*H$_2$), 49.6 (*C*H), 126.5 (*C*H), 127.2 (*C*H), 127.8 (*C*H), 128.7 (*C*H), 132.8 (*C*H), 136.8 (*C*), 180.4 (*C*(O)); *m/z* LRMS (ESI−) 173 (M-CO_2H^-, 64%), 217 (M-H$^-$, 42); HRMS (ESI+) found [M+Na]$^+$ 241.1195; [$C_{14}H_{18}NaO_2$]$^+$ requires 249.1199.

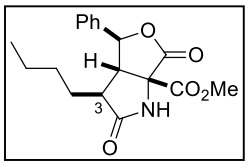
*(*E*)-Dimethyl 2-(2-butyl-4-phenylbut-3-enamido)malonate* 9d



Prepared from (*E*)-2-butyl-4-phenylbut-3-enoic acid **S12** (200 mg, 0.916 mmol) and dimethyl aminomalonate hydrochloride **S2** (185 mg, 1.01 mmol) using General Procedure B and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-butyl-4-phenylbut-3-enamido)malonate* **9d** as a white solid (174 mg, 0.500 mmol, 55%); *m.p.* 216–218 °C; R_f = 0.29 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3314m (N−H), 2957m (C−H), 2926m (C−H), 1763s (C=O malonate), 1744s (C=O malonate), 1651s (C=O amide I), 1536s (C=O amide II); δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* = 6.7, H_3CCH_2), 1.15–1.44 (4H, m, H$_3$CC*H*$_2$C*H*$_2$), 1.55–1.70 (1H, m, *n*PrC*H*H'), 1.87–1.97 (1H, m, *n*PrCH*H*'), 3.02–3.20 (1H, m, *n*BuC*H*C(O)), 3.81 (3H, s, CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 5.20 (1H, d, *J* = 6.8, C*H*NH), 6.21 (1H, dd, *J* = 15.9, 8.3, PhCH=C*H*), 6.54 (1H, d, *J* = 15.9, PhC*H*=CH), 6.60 (1H, br d, *J* = 6.8, N*H*), 7.20–7.45 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 22.7 (*C*H$_2$), 29.4 (*C*H$_2$), 32.1 (*C*H$_2$), 50.8 (*C*H), 53.6 (*C*H$_3$), 53.6 (*C*H$_3$), 56.3 (*C*H), 126.5 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 128.7 (*C*H), 133.1 (*C*), 136.8 (*C*H), 166.8 (*C*(O)), 166.9 (*C*(O)), 173.5 (*C*(O)); *m/z* LRMS (ESI+) 348 (M+H$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$

370.1619; $[C_{19}H_{25}NNaO_5]^+$ requires 370.1625. *Yield over two steps from carboxylic acid* **S1**: 980 mg, 2.82 mmol, 50%.

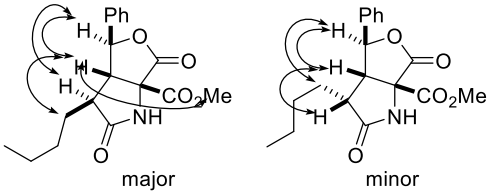
(3S,3aS*,4S*,6aS*)-Methyl 3-butyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* 10d



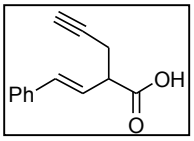
Formed as a 9:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-styrylhexanamido)malonate **9d** (104 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3a*S**,4S*,6a*S**)-methyl 3-butyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10d** as a white solid (64.5 mg, 0.195 mmol, 65%); *m.p.* 78–82 °C; R_f = 0.22 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3345m (N−H), 2956m (C−H), 1748s (C=O γ-lactone), 1712s (C=O ester), 1681m (C=O γ-lactam); δ_H (500 MHz, $CDCl_3$) 0.80 (3H, t, *J* = 6.9, H_3CCH_2), 1.09−1.29 (4H, m, $H_3CCH_2CH_2$), 1.30−1.49 (1H, m, *n*PrC*H*H'), 1.71−1.81 (1H, m, *n*PrCH*H'*), 2.59 (1H, ddd, *J* = 8.9, 5.2, 1.5,C*H*C(O)), 3.14 (1H, dd, *J* = 6.9, 1.5, PhCHC*H*), 3.86 (3H, s, CO_2CH_3), 5.29 (1H, d, *J* = 6.9, PhC*H*), 6.88 (1H, br s, N*H*), 7.37−7.62 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 13.8 (CH_3), 22.2 (CH_2), 29.1 (CH_2), 31.0 (CH_2), 47.2 (*C*H), 54.0 (*C*H), 54.1 (CH_3), 68.6 (*C*), 86.2 (*C*H), 125.8 (*C*H), 129.3 (*C*H), 129.5 (*C*H), 137.1 (*C*), 168.8 (*C*(O)), 170.2 (*C*(O)), 177.5 (*C*(O)); *m/z* LRMS (ESI−) 330 ($M-H^-$, 100%); HRMS (ESI+) found $[M+Na]^+$ 354.1311; $[C_{18}H_{21}NNaO_5]^+$ requires 354.1312.

From the mixture of diastereomers it was possible to assign the partial ^{1}H NMR and ^{13}C NMR spectra for the minor diastereomer; δ_H (500 MHz, $CDCl_3$) 0.67 (3H, t, *J* = 7.2, H_3CCH_2), 2.63 (1H, ddd, 7.6, 5.9, 4.4 C*H*C(O)), 3.67 (1H, t, *J* = 7.8, PhCHC*H*), 3.95 (3H, s, CO_2CH_3), 5.36(1H, d, *J* = 8.6, PhC*H*), 6.78 (1H, br s, N*H*), 7.37−7.62 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 13.7, 22.4, 43.8, 51.6, 68.2, 82.1, 127.7, 129.3, 130.1, 136.6, 168.3, 169.3, 176.3.

Key nOe data:

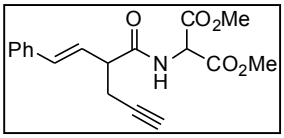


*(*E*)-2-Propargyl-4-phenylbut-3-enoic acid* S13



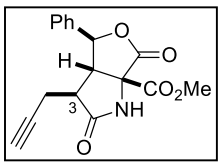
Prepared from *trans*-styrylacetic acid **S1** (1.00 g, 6.17 mmol) and propargyl bromide (2.75 mL, 18.5 mmol) using General Procedure A and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate + 1% acetic acid), then recrystallization (dichloromethane/hexane), which gave *(*E*)-2-Propargyl-4-phenylbut-3-enoic acid* **S13** as a white crystalline solid (226 mg, 1.13 mmol, 36%); *m.p.* 88–90 °C; ν_{max} (thin film) 3280s (H–C≡C), 3105br (O-H), 3027m (C−H), 1697vs (C=O acid), 1416m; δ_H (400 MHz, $CDCl_3$) 2.06 (1H, t, *J* = 2.1, *H*C≡C), 2.62 (1H, ddd, *J* = 16.8, 7.2, 2.1, HC≡CC*H*H'CH), 2.75 (1H, ddd, *J* = 16.8, 7.0, 2.1, HC≡CCH*H*'CH), 3.46 (1H, ddd, *J* = 8.5, 7.2, 7.0, PhCH=CHC*H*), 6.23 (1H, dd, *J* = 15.9, 8.5, PhCH=C*H*CH), 6.63 (1H, d, *J* = 15.9, PhC*H*=CH), 7.15–7.50 (5H, m, Ar*H*) 11.4 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 22.0 (CH_2), 48.3 (*C*H), 70.8 (*C*H), 80.7 (*C*), 124.7 (*C*H), 126.7 (*C*H), 128.1 (*C*H), 128.7 (*C*H), 134.2 (*C*H), 136.4 (*C*), 178.7 (*C*(O)); *m/z* LRMS (ESI−) 155 ($M-CO_2H^-$, 100%), 199 ($M-H^-$, 61); HRMS (ESI−) found $[M-H]^-$ 199.0758; $[C_{13}H_{11}O_2]^+$ requires 199.0765.

*(*E*)-Dimethyl 2-(2-propargyl-4-phenylbut-3-enamido)malonate* **9e**



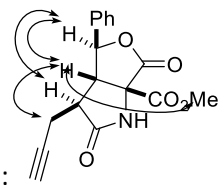
Prepared from (*E*)-2-propargyl-4-phenylbut-3-enoic acid **S13** (150 mg, 0.750 mmol) and dimethyl aminomalonate hydrochloride **S2** (151 mg, 0.820 mmol) using General Procedure B and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-propargyl-4-phenylbut-3-enamido)malonate* **9e** as a white solid (113 mg, 0.34 mmol, 46%); *m.p.* 104–105 °C; ν_{max} (thin film) 3299m (H–C≡C and N-H), 2956w (C–H), 1756s (C=O malonate), 1743s (C=O malonate), 1653s (C=O amide I), 1538m (C=O amide II); δ_H (400 MHz, $CDCl_3$) 2.05 (1H, t, *J* = 2.6, *H*C≡C), 2.63 (1H, ddd, *J* = 16.9, 7.1, 2.6, HC≡CC*H*H'CH), 2.76 (1H, ddd, *J* = 16.9, 6.2, 2.6, HC≡CCH*H*'CH), 3.34 (1H, ddd, *J* = 8.8, 7.1, 6.2, PhCH=CHC*H*), 3.81 (3H, s, CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 5.21 (1H, d, *J* = 6.8, C*H*NH), 6.28 (1H, dd, *J* = 15.9, 8.8, PhCH=C*H*), 6.67 (1H, d, *J* = 15.9, PhC*H*=CH), 6.48 (1H, br d, *J* = 6.8, N*H*), 7.17–7.48 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (CH_2), 49.2 (*C*H), 53.7 (CH_3), 56.4 (*C*H), 70.8 (*C*H), 81.3 (*C*), 125.5 (*C*H), 126.7 (*C*H), 128.2 (*C*H), 128.8 (*C*H), 134.8 (*C*), 136.4 (*C*H), 166.6 (*C*(O)O), 166.6 (*C*(O)O), 171.6 (*C*(O)N); *m/z* LRMS (ESI+) 352 ($M+Na^+$, 40%), 681 ($2M+Na^+$, 100); HRMS (ESI+) found $[M+Na]^+$ 352.1150; $[C_{18}H_{19}NNaO_5]^+$ requires 352.1155. *Yield over two steps from carboxylic acid* **S1**: 1.12 g, 3.40 mmol, 55%.

(3S,3aS*,4S*,6aS*)-Methyl 2,6-dioxo-4-phenyl-3-(prop-2-ynyl)hexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10e**

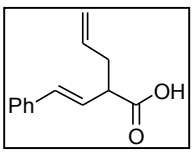


Formed as an 18:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-propargyl-4-phenylbut-3-enamido)malonate **9e** (98.7 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3*R**,3*aR**,4*R**,6*aR**)-methyl 2,6-dioxo-4-phenyl-3-(prop-2-ynyl)hexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a*-carboxylate* **10e** as a white solid (71.4 mg, 0.228 mmol, 76%); *m.p.* 164–165 °C, R_f = 0.25 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3288m (C≡C–H and N-H), 1783s (C=O *γ*-lactone), 1757s (C=O ester), 1719s (C=O *γ*-lactam); δ_H (500 MHz, CD_2Cl_2) 1.96 (1H, t, *J* = 2.7, C≡C*H*), 2.50 (1H, ddd, *J* = 17.1, 8.4, 2.7, HC≡CC*H*H'), 2.65 (1H, ddd, J = 17.1, 4.8, 2.7, HC≡CCH*H*'), 2.87 (1H, ddd, *J* = 8.4, 4.8, 3.4, C*H*C(O)), 3.45 (1H, dd, *J* = 5.4, 3.4, PhCHC*H*), 3.79 (3H, s, CO_2CH_3), 5.45 (d, *J* = 5.4, PhC*H*), 6.75 (1H, br s, N*H*), 7.37–7.47 (5H, m, Ar*H*); δ_C (126 MHz, CD_2Cl_2) 20.6 (CH_2), 46.9 (*C*H), 52.5 (*C*H), 53.9 (CH_3), 67.9 (*C*H), 71.2 (*C*), 79.7 (*C*), 86.2 (*C*H), 125.9 (*C*H), 129.0 (*C*H), 129.3 (*C*H), 137.4 (*C*), 168.2 (*C*(O)), 170.3 (*C*(O)), 174.8 (*C*(O)); *m/z* LRMS (ESI+) 336 ($M+Na^+$, 100%); HRMS (ESI+) 336.0842; $[C_{17}H_{15}NNaO_5]^+$ requires 336.0842.

Key nOe data:



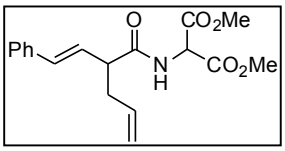
*(*E*)-2-Allyl-4-phenylbut-3-enoic acid* **S14**



Prepared from *trans*-styrylacetic acid **S1** (1.00 g, 6.17 mmol) and allyl chloride (1.42 g, 18.5 mmol) using General Procedure A and purified by flash column chromatography (3:1 petroleum ether 40–60 °C:ethyl acetate), then recrystallization (dichloromethane/isohexane), which gave *(*E*)-2-allyl-4-phenylbut-3-enoic acid* **S14** as a white crystalline solid (795 mg, 3.67 mmol, 60%); *m.p.* 41–43 °C; R_f = 0.18 (1:1

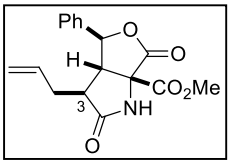
petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3025 brm (O-H), 1697s (C=O); δ_H (400 MHz, $CDCl_3$) 2.46 (1H, ddd, *J* = 14.2, 7.0, 7.0, C*H*H'CHCO$_2$H), 2.64 (1H, ddd, *J* = 14.2, 7.2, 7.2, CH*H*'CHCO$_2$H), 3.28–3.35 (1H, m, C*H*CO$_2$H), 5.09 (1H, dddd, *J* = 10.2, 1.9, 0.8, 0.8, CH$_2$CH=C*H*H), 5.14 (1H, ddd, *J* = 17.1, 3.0, 1.4, CH$_2$CH=CH*H*), 5.81 (1H, dddd, *J* = 17.1, 10.2, 7.2, 7.0, CH$_2$C*H*=CH$_2$), 6.21 (1H, dd, *J* = 8.8, 15.9, PhCH=C*H*), 6.54 (1H, d, *J* = 15.9, PhC*H*=CH), 7.15–7.46 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 36.7 (*C*H$_2$), 49.2 (*C*H), 117.7 (*C*H$_2$), 126.3 (*C*H), 126.6 (*C*H), 127.9 (*C*H), 128.7 (*C*H$_2$), 133.2 (*C*H), 134.6 (*C*H), 136.7 (*C*H), 179.1 (*C*(O)); *m/z* LRMS (ESI+) 201 (M-H$^-$, 20%); HRMS (ESI+) found [M+Na]$^+$ 225.0882; [$C_{13}H_{14}NaO_2$]$^+$ requires 225.0886.

*(*E*)-Dimethyl 2-(2-allyl-4-phenylbut-3-enamido)malonate* 9f



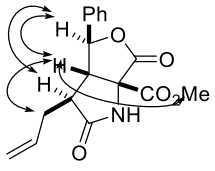
Prepared from (*E*)-2-allyl-4-phenylbut-3-enoic acid **S14** (152 mg, 0.750 mmol) and dimethyl aminomalonate hydrochloride **S2** (152 mg, 0.825 mmol) using General Procedure B and purified by flash column chromatography (5→3:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-allyl-4-phenylbut-3-enamido)malonate* **9f** as a white solid (153 mg, 0.461 mmol, 61%); *m.p.* 62–63 °C; R_f = 0.27 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3301m (N−H), 2955m (C−H), 1761s (C=O malonate), 1747s (C=O malonate), 1661s (C=O amide I), 1516s (C=O amide II); δ_H (400 MHz, $CDCl_3$) 2.44 (1H, ddd, *J* = 14.2, 7.2, 7.2, H$_2$C=CHC*H*H), 2.67 (1H, ddd, *J* = 14.2, 7.0, 6.9, H$_2$C=CHCH*H*), 3.18 (1H, ddd, *J* = 8.8, 7.2, 6.9, AllC*H*C(O)), 3.81 (3H, s, CO$_2$C*H*$_3$), 3.82 (3H, s, CO$_2$C*H*$_3$), 5.04–5.17 (2H, m, *H*$_2$C=CHCH$_2$), 5.20 (1H, d, *J* = 6.7, C*H*NH), 5.80 (1H, dddd, *J* = 17.1, 10.1, 7.2, 7.0, H$_2$C=C*H*CH$_2$), 6.22 (1H, dd, *J* = 15.9, 8.8, PhCH=C*H*), 6.57 (1H, d, *J* = 15.9, PhC*H*=CH), 6.66 (1H, br d, *J* = 6.7, N*H*), 7.21–7.43 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 36.6 (*C*H$_2$), 50.3 (*C*H), 53.6 (*C*H$_3$), 53.6 (*C*H$_3$), 56.3 (*C*H), 117.5 (*C*H$_2$), 126.5 (*C*H), 127.0 (*C*H), 127.9 (*C*H), 128.7 (*C*H), 133.6 (*C*H), 135.1 (C*H*), 136.6 (*C*), 166.7 (*C*(O)), 166.8 (*C*(O)), 172.7 (*C*(O)); *m/z* LRMS (ESI+) 332 (M+H$^+$, 85%), 354 (M+Na$^+$, 20), 680 (2M+NH$_4^+$, 91), 685 (2M+Na$^+$, 100); HRMS (ESI+) found [M+Na]$^+$ 354.1307; [$C_{18}H_{21}NNaO_5$]$^+$ requires 354.1312. *Yield over two steps from carboxylic acid* **S1**: 930 mg, 2.81 mmol, 46%.

(3S,3aS*,4S*,6aS*)-Methyl 3-allyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* 10f

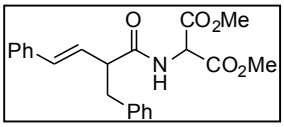


Formed as a 19:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-allyl-4-phenylbut-3-enamido)malonate **9f** (99.3 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3*aS**,4S*,6*aS**)-methyl 3-allyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6*a*-carboxylate* **10f** as a white solid (69.9 mg, 0.222 mmol, 74%); *m.p.* 110–113 °C; R_f = 0.20 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3218 brm (N−H), 2957m (C−H), 1782s (C=O γ-lactone), 1759s (C=O ester), 1715s (C=O γ-lactam); δ_H (500 MHz, $CDCl_3$) 2.26 (1H, ddd, *J* = 14.8, 8.7, 7.1, H$_2$C=CHC*H*H'CH), 2.47–2.54 (1H, m, H$_2$C=CHCH*H*'CH), 2.73 (1H, ddd, *J* = 8.7, 4.5, 2.1, H$_2$C=CHCH$_2$C*H*), 3.22 (1H, ddd, *J* = 6.7, 2.1, 0.6, PhCHC*H*CH), 3.83 (3H, s, CO$_2$C*H*$_3$), 4.98 (1H, dd, *J* = 17.1, 1.3, *H*H'C=CHCH$_2$), 5.01 (1H, dd, *J* = 10.2, 1.3, H*H*'C=CHCH$_2$), 5.33 (1H, d, *J* = 6.7, PhC*H*), 5.60 (1H, dddd, *J* = 17.1, 10.2, 7.1, 7.1, H$_2$C=C*H*CH$_2$), 7.36–7.49 (5H, m, Ar*H*), 7.49 (1H, br s, N*H*); δ_C (126 MHz, $CDCl_3$) 35.2 (*C*H$_2$), 46.9 (*C*H), 52.7 (*C*H$_3$), 53.9 (*C*H), 68.6 (*C*), 85.9 (*C*H), 119.0 (*C*H$_2$), 125.9 (*C*H), 129.1 (*C*H), 129.5 (*C*H), 133.5 (*C*H), 137.1 (*C*), 168.6

(*C*(O)), 170.1 (*C*(O)), 177.1 (*C*(O)); *m/z* LRMS (ESI−) 314 (M-H$^-$, 100%); HRMS (ESI+) found [M+Na]$^+$ 338.1003; [$C_{17}H_{17}NNaO_5$]$^+$ requires 338.0999.

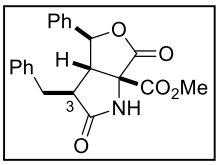
Key nOe data: 

*(*E*)-Dimethyl 2-(2-benzyl-4-phenylbut-3-enamido)malonate* 9g



Prepared from (*E*)-2-benzyl-4-phenylbut-3-enoic acid **S5** (100 mg, 0.396 mmol) and dimethyl aminomalonate hydrochloride **S2** (80 mg, 0.436 mmol) using General Procedure B and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-benzyl-4-phenylbut-3-enamido)malonate* **9g** as a white solid (94 mg, 0.246 mmol, 62%); *m.p.* 64–68 °C; R_f = 0.33 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3314m (N−H), 1760s (C=O malonate), 1747s (C=O malonate), 1661s (C=O amide I), 1526s (C=O amide II); δ_H (400 MHz, $CDCl_3$) 2.94 (1H, dd, *J* = 13.5, 7.3, PhC*H*H'CH), 3.27 (1H, dd, *J* = 13.5, 7.0, PhCH*H*'CH), 3.37 (1H, ddd, *J* = 8.6, 7.3, 7.0, $PhCH_2CHC(O)$), 3.78 (3H, s, CO_2CH_3), 3.79 (3H, s, CO_2CH_3), 5.17 (1H, d, *J* = 6.8, C*H*NH), 6.24 (1H, dd, *J* = 15.9, 8.6, PhCH=C*H*CH), 6.46 (1H, d, *J* = 15.9, PhC*H*), 6.54 (1H, br d, *J* = 6.8, N*H*), 7.26–7.44 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 38.6 (CH_2), 52.6 (*C*H), 53.6 (CH_3), 53.6 (CH_3), 56.3 (*C*H), 126.5 (*C*H), 126.5 (*C*H), 127.0 (*C*H), 127.9 (*C*H), 128.5 (*C*H), 128.7 (*C*H), 129.3 (*C*H), 133.6 (*C*H), 136.7 (*C*), 138.9 (*C*), 166.6 (*C*(O)), 166.7 (*C*(O)), 172.6 (*C*(O)); *m/z* LRMS (ESI−) 380 (M-H$^-$, 100%); HRMS (ESI+) found [M+Na]$^+$ 404.1463; [$C_{22}H_{23}NNaO_5$]$^+$ requires 404.1468. *Yield over two steps from carboxylic acid* **S1**: 1.04 g, 2.73 mmol, 44%.

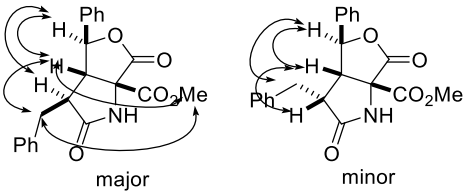
(3S,3aS*,4S*,6aS*)-Methyl 3-benzyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* 10g



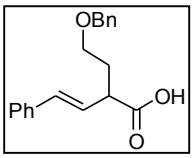
Formed as an 11:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-benzyl-4-phenylbut-3-enamido)malonate **9g** (114 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3a*S**,4*S**,6a*S**)-methyl 3-benzyl-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10g** as a white solid (95.3 mg, 0.261 mmol, 87%); *m.p.* 51–52 °C, R_f = 0.19 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3423 brm (N−H), 1783s (C=O *γ*-lactone), 1756s (C=O ester), 1712s (C=O *γ*-lactam); δ_H (500 MHz, $CDCl_3$) 2.67 (1H, dd, *J* = 14.0, 10.1, PhC*H*H'CH), 2.98 (1H, ddd, *J* = 10.1, 4.5, 2.8, $PhCH_2CH$), 3.18 (1H, dd, *J* = 6.2, 2.8, PhCHC*H*CH), 3.25 (1H, dd, *J* = 14.0, 4.5, PhCH*H*'CH), 3.73 (3H, s, CO_2CH_3), 5.22 (1H, d, *J* = 6.2, PhC*H*CHCH), 6.87–7.43 (10H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 36.8 (CH_2), 49.8 (*C*H), 52.0 (*C*H), 54.0 (CH_3), 68.0 (*C*), 86.0 (*C*H), 125.4 (CH), 127.3 (CH), 128.6 (*C*H), 129.1 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 136.9 (*C*), 137.0 (*C*), 168.2 (*C*(O)), 170.2 (*C*(O)), 176.4 (*C*(O)); *m/z* LRMS (ESI+) 366 (M+H$^+$, 70%), 388 (M+Na$^+$, 55), 731 (2M+H$^+$, 40), 748 (2M+NH_4^+, 100), 753 (2M+Na$^+$, 75); HRMS (ESI+) found [M+Na]$^+$ 388.1157; [$C_{21}H_{19}NNaO_5$]$^+$ requires 388.1155.

From the mixture of diastereomers it was possible to assign the ^{1}H NMR and ^{13}C NMR spectra for the minor diastereomer; δ_H (500 MHz, $CDCl_3$) 2.64 (1H, dd, *J* = 15.1, 10.6, PhC*H*H'CH), 3.05 (1H, ddd, *J* = 10.6, 7.4, 3.5, $PhCH_2CH$), 3.41(1H, dd, *J* = 15.1, 3.5, PhCH*H*'CH), 3.71-3.75 (1H, m, , PhCHC*H*CH), 3.91 (3H, s, CO_2CH_3), 5.47 (1H, d, *J* = 8.3, PhC*H*CHCH), 6.87–7.43 (10H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 30.7 ,45.3, 50.4, 54.0, 67.8, 82.2, 126.4, 127.9, 128.1, 128.4, 129.1, 130.0, 135.8, 138.0, 167.8, 169.1, 175.3.

Key nOe data:

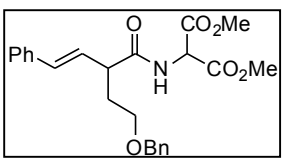


*(*E*)-2-(2-(Benzyloxy)ethyl)-4-phenylbut-3-enoic acid* S15



To a stirred solution of diisopropylamine (2.83 mL, 21.0 mmol) in tetrahydrofuran (9.0 mL) was added dropwise at 0 °C *n*-butyllithium (12.5 mL, 1.6 M solution in hexane). The solution was stirred for 15 min at 0 °C, then a solution of *trans*-styrylacetic acid **S1** (1.62 g, 10.0 mmol) in tetrahydrofuran (7.0 mL) was added dropwise, followed by dropwise addition of ((2-iodoethoxy)methyl)benzene **S6** (2.88 g, 11.0 mmol). The mixture was stirred at 0 °C for a further 1 h, then allowed to warm to room temperature and stirred for 16 h. The reaction was then quenched with water (10 mL) and extracted with ethyl acetate (2×50 mL) and the organic layers discarded. The aqueous layer was then acidified using pH 2 sulfate buffer and re-extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (2×50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate + 1% acetic acid), then recrystallised (dichloromethane/hexane), which gave *(*E*)-2-(2-(benzyloxy)ethyl)-4-phenylbut-3-enoic acid* **S15** as a white crystalline solid (434 mg, 1.47 mmol, 15%); *m.p.* 97–98 °C; ν_{max} (thin film) 3107br (O-H), 1704m (C=O carboxylic acid); δ_H (400 MHz, $CDCl_3$) 1.93 (1H, dddd, *J* = 13.4, 7.3, 5.5, 5.5, $BnOCH_2CH$H'CH), 2.19–2.29 (1H, m, $BnOCH_2CH$H'CH), 3.46 (1H, ddd, *J* = 9.0, 7.3, 7.0, PhCH=CHC*H*), 3.50–3.61 (2H, m, $BnOCH_2$), 4.48 (1H, d, *J* = 11.9, PhC*H*H'O), 4.53 (1H, d, *J* = 11.9, PhCH*H*'O), 6.18 (1H, dd, *J* = 15.9, 9.0, PhCH=C*H*CH), 6.52 (1H, d, *J* = 15.9, PhC*H*=CHCH), 7.20–7.43 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 32.2 (CH_2), 46.1 (CH), 67.2 (CH_2), 73.0 (CH_2), 126.2 (CH), 126.4 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 128.4 (CH), 128.5 (CH), 133.3 (CH), 136.6 (C), 138.2 (C), 179.4 (C(O)); *m/z* LRMS (ESI+) 319 ($M+Na^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 319.1304; $[C_{19}H_{20}NaO_3]^+$ requires 319.1305.

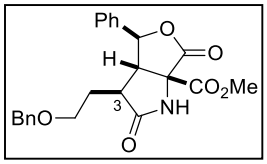
*(*E*)-Dimethyl 2-(2-(2-(benzyloxy)ethyl)-4-phenylbut-3-enamido)malonate* 9h



Prepared from (*E*)-2-(2-(benzyloxy)ethyl)-4-phenylbut-3-enoic acid **S15** (150 mg, 0.507 mmol) and dimethyl aminomalonate hydrochloride **S2** (102 mg, 0.557 mmol) using General Procedure B and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*E*)-dimethyl 2-(2-(2-(benzyloxy)ethyl)-4-phenylbut-3-enamido)malonate* **9h** as a white crystalline solid (146 mg, 0.343 mmol, 68%); *m.p.* 53–56 °C; ν_{max} (thin film) 3311m (N–H), 2955m (C–H), 1761s (C=O malonate), 1747s (C=O malonate), 1669m (C=O amide I); δ_H (400 MHz, $CDCl_3$)

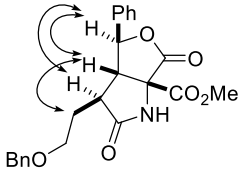
1.86–1.97 (1H, m, BnOCH$_2$C*H*H'CH), 2.22 (1H, dddd, *J* = 12.4, 6.2, 6.2, 6.0, BnOCH$_2$CH*H*'CH), 3.39 (1H, ddd, *J* = 9.0, 7.6, 6.0, PhCH=CHC*H*), 3.46–3.68 (2H, m, BnOC*H*$_2$CH$_2$), 3.81 (3H, s, CO$_2$C*H*$_3$), 3.82 (3H, s, CO$_2$C*H*$_3$), 4.48 (1H, d, *J* = 11.8, PhC*H*HO), 4.56 (1H, d, *J* = 11.8, PhCH*H*O), 5.19 (1H, d, *J* = 6.7, NHC*H*), 6.22 (1H, dd, *J* = 16.0, 9.0, PhCH=C*H*CH), 6.53 (1H, d, *J* = 16.0, PhC*H*=CHCH), 6.75 (1H, br d, *J* = 6.7, N*H*), 7.21–7.39 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 32.5 (*C*H$_2$), 47.1 (*C*H), 53.5 (*C*H$_3$), 53.6 (*C*H$_3$), 56.3 (*C*H), 67.3 (*C*H$_2$), 73.2 (*C*H$_2$), 126.5 (*C*H), 127.3 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 128.0 (*C*H), 128.5 (*C*H), 128.7 (*C*H), 133.3 (*C*H), 136.8 (*C*), 138.5 (*C*), 166.7 (*C*(O)), 166.8 (*C*(O)), 173.3 (*C*(O)); *m/z* (ESI+) LRMS 448 (M+Na$^+$, 77%), 873 (2M+Na$^+$, 100); HRMS (ESI+) found [M+Na]$^+$ 448.1731; [$C_{24}H_{27}NNaO_6$]$^+$ requires 448.1731. *Yield over two steps from carboxylic acid* **S1**: 769 mg, 1.81 mmol, 29%.

(3S,3aS*,4S*,6aS*)-Methyl 3-(2-(benzyloxy)ethyl)-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* 10h

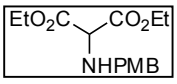


Formed as a 25:1 mixture of C-3 epimers from (*E*)-dimethyl 2-(2-(2-(benzyloxy)ethyl)-4-phenylbut-3-enamido)malonate **9h** (128 mg, 0.300 mmol) using General Procedure C and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3S*,3*aS**,4S*,6*aS**)-methyl 3-(2-(benzyloxy)ethyl)-2,6-dioxo-4-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* **10h** as a viscous colourless oil (85.9 mg, 0.210 mmol, 70%); R_f = 0.36 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3224m (N-H), 2862m (C-H), 1783s (C=O *γ*-lactone), 1758s (C=O ester), 1715s (C=O *γ*-lactam); δ_H (500 MHz, $CDCl_3$) 1.59–1.78 (1H, m, BnOCH$_2$C*H*H'CH), 2.15 (1H, ddt, *J* = 14.6, 7.2, 4.6, BnOCH$_2$CH*H*'CH), 2.82 (1H, ddd, *J* = 9.3, 4.6, 2.7, PhCHCHC*H*), 3.42–3.54 (3H, m, BnOC*H*$_2$CH$_2$ and PhCHC*H*CH), 3.71 (3H, s, CO$_2$C*H*$_3$), 4.28 (2H, s, PhC*H*$_2$O), 5.35 (1H, d, *J* = 6.3, PhC*H*CHCH), 7.11 (1H, br s, N*H*), 7.13–7.27 (10H, Ar*H*); δ_C (126 MHz, $CDCl_3$) 31.0 (*C*H$_2$), 45.4 (*C*H), 53.4 (*C*H), 53.8 (*C*H$_3$), 67.7 (*C*H$_2$), 68.2 (*C*), 73.0 (*C*H$_2$), 86.2 (*C*H), 125.8 (*C*H), 127.5 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 129.1 (*C*H), 129.3 (*C*H), 137.3 (*C*), 137.9 (*C*), 168.6 (*C*(O)), 170.4 (*C*(O)), 177.3 (*C*(O)); *m/z* LRMS (ESI+) 432 (M+Na$^+$, 68%), 841 (2M+Na$^+$, 100); HRMS (ESI+) found [M+Na$^+$] 432.1419; [$C_{23}H_{23}NNaO_6$]$^+$ requires 432.1418.

Key nOe data:



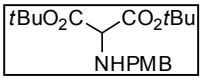
Diethyl 2-((4-methoxybenzyl)amino)malonate S16



To a stirred solution of diethyl bromomalonate (2.34 g, 10.0 mmol) in $CHCl_3$ (45 mL) was added NEt_3 (2.80 mL, 20.0 mmol) and *para*-methoxylbenzylamine (2.54 mL, 19.5 mmol) and the solution was heated under reflux overnight. After cooling to RT, the reaction was quenched with H_2O (45 mL) and extracted with $CHCl_3$ (2×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (2:1 petroleum ether 30–40:diethyl ether), which gave diethyl *2-((4-methoxybenzyl)amino)malonate* **S16** as a pale yellow oil (525 mg, 1.97 mmol, 20%); R_f 0.15 (3:1 petroleum ether 40–60:ethyl acetate); ν_{max} (thin film) 3320w (N-H), 1934s (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (6H, t, *J* = 7.2, (CO$_2$CH$_2$C*H*$_3$)$_2$), 2.43 (1H, br s, N*H*), 3.77 (2H, s, NC*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 4.06 (1H, s, C*H*(CO$_2$Et)$_2$), 4.25 (3H, q, *J* = 7.2, CO$_2$C*H*$_2$CH$_3$), 4.25 (3H, q, *J* = 7.2, CO$_2$C*H*'$_2$CH$_3$), 6.88 (2H, d, *J* = 8.6, Ar*H*), 7.27 (2H, d, *J* = 8.6, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 50.8 (*C*H$_2$), 54.9 (*C*H$_3$), 61.5

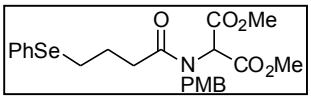
(CH_2), 63.7 (*C*H), 113.6 (*C*H), 129.4 (*C*H), 130.6 (*C*), 158.7 (*C*), 168.3 (*C*); *m/z* LRMS (ESI+) 296 ($M+H^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 318.1298; $[C_{15}H_{21}NNaO_5]^+$ requires 318.1312.

Di-tert-*butyl 2-(4-methoxybenzylamino)malonate* 22



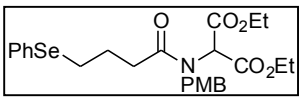
A stirred solution of di-*tert*-butyl bromomalonate **S8** (5.00 g, 16.9 mmol), 4-methoxybenzylamine (4.43 mL, 33.9 mmol) and triethylamine (4.72 mL, 33.9 mmol) in chloroform (75 mL) was heated under reflux for 16 h. The reaction mixture was allowed to cool and diluted with water (75 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (4:1 petroleum ether 40–60 °C:diethyl ether), which gave *di*-tert-*butyl 2-(4-methoxybenzylamino)malonate* **22** as a colourless oil (3.24 g, 9.21 mmol, 55%); R_f = 0.34 (4:1 petroleum ether 40–60 °C:diethyl ether); ν_{max} (thin film) 3346brm (N−H), 2979s (C−H), 1749s (C=O malonate), 1734s (C=O malonate); δ_H (400 MHz, $CDCl_3$) 1.47 (18H, s, C(CH_3)$_3$), 2.21 (1H, br s, N*H*), 3.73 (2H, s, ArCH_2), 3.80 (3H, s, OCH_3), 3.84 (1H, s, C*H*(CO_2*t*Bu)$_2$), 6.86 (2H, d*, J* = 8.5, Ar*H*), 7.27 (2H, d*, J* = 8.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (CH_3), 50.9 (CH_2), 55.4 (CH_3), 65.6 (*C*H), 82.2 (*C*), 113.9 (*C*H), 129.8 (*C*H), 131.3 (*C*), 159.0 (*C*), 168.0 (*C*(O)); *m/z* LRMS (ESI+) 352 ($M+H^+$, 96%), 374 ($M+Na^+$, 48), 703 ($2M+H^+$, 72), 725 ($2M+Na^+$, 100); HRMS (ESI+) found $[M+H]^+$ 352.2124; $[C_{19}H_{30}NO_5]^+$ requires 352.2118.

*Dimethyl 2-(*N-*(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate* S17



Prepared from 4-(phenylselanyl)butanoic acid **18** (271 mg, 1.11 mmol) and dimethyl 2-((4-methoxybenzyl)amino)malonate **S7** (274 mg, 0.928 mmol) using General Procedure D to and purified by flash column chromatography (1:1 petroleum ether 40–60 °C:ethyl acetate), which gave *dimethyl 2-(*N-*(4-methoxylbenzyl)-4-(phenylselanyl)butanamido)malonate* **S17** as a colourless oil (393 mg, 0.799 mmol, 86%); R_f = 0.27 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2952w (C-H), 1743s (ester C=O), 1658s (amide C=O); δ_H (500 MHz, $CDCl_3$) 2.03–2.10 (2H, m, $CH_2CH_2CH_2$), 2.55 (2H, t, *J* = 7.1, CH_2C(O)), 2.96 (2H, t, *J* = 7.1, PhSeCH_2), 3.65 (6H, s, (CO_2CH_3)$_2$), 3.81 (3H, s, OCH_3), 4.61 (2H, s, NCH_2), 5.31 (1H, s, C*H*(CO_2Me)$_2$), 6.88 (2H, d, *J* = 8.7, Ar*H*), 7.14–7.18 (2H, m, Ar*H*), 7.21–7.26 (3H, m, Ar*H*), 7.43–7.47 (2H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 25.4 (CH_2), 27.3 (CH_2), 32.7 (CH_2), 50.8 (CH_2), 52.9 (CH_3), 55.4 (CH_3), 61.0 (*C*H), 114.3 (*C*H), 126.9 (*C*H), 128.0 (*C*H), 129.2 (*C*H), 130.1 (*C*), 132.7 (*C*H), 159.3 (*C*), 166.8 (*C*), 173.7 (*C*); *m/z* LRMS (ESI+) 516 ($M+Na^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 516.0891; $[C_{23}H_{27}NNaO_5Se]^+$ requires 516.0897.

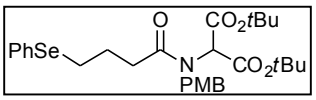
*Diethyl 2-(*N-*(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate* S18



Prepared from 4-(phenylselanyl)butanoic acid **18** (458 mg, 1.88 mmol) and aminomalonate **S16** (463 mg, 1.57 mmol) using General Procedure D to and purified by flash column chromatography (5:1 petroleum ether 40–60 °C:ethyl acetate), which gave *diethyl 2-(*N-*(4-methoxylbenzyl)-4-(phenylselanyl)butanamido)malonate* **S18** as a colourless oil (694 mg, 1.33 mmol, 85%); R_f = 0.21 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2980w (C-H), 1737s (ester C=O), 1658s (amide C=O); δ_H (500 MHz, $CDCl_3$) 1.21 (6H, t, *J* = 7.1, ($CO_2CH_2CH_3$)$_2$), 2.02–2.09 (2H, m, $CH_2CH_2CH_2$), 2.52 (2H, t, *J* = 7.1, CH_2CH_2C(O)), 2.94 (2H, t, *J* = 7.0, PhSeCH_2), 3.80 (3H, s, OCH_3), 4.06 (2H, dq, *J* = 10.7, 7.1, ($CO_2CHH'CH_3$)$_2$), 4.15 (2H, dq, *J* = 10.7, 7.1, ($CO_2CHH'CH_3$)$_2$), 4.62 (2H, s, NCH_2), 5.33 (1H, s, C*H*(CO_2Et)$_2$), 6.87 (2H, d, *J* = 8.9, Ar*H*), 7.14–7.19 (2H, m, Ar*H*), 7.20–7.25 (3H, m, Ar*H*), 7.42–7.46 (2H,

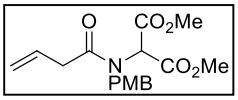
m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 14.0 (*C*H_3), 25.4 (*C*H_2), 27.3 (*C*H_2), 32.8 (*C*H_2), 50.6 (*C*H_2), 55.4 (*C*H_3), 61.3 (*C*H), 62.1 (*C*H_2), 114.2 (*C*H), 126.9 (*C*H), 127.9 (*C*H), 128.3 (*C*H), 129.1 (*C*), 130.0 (*C*), 132.6 (*C*H), 159.2 (*C*), 166.3 (*C*(O)), 173.7 (*C*(O)); *m/z* LRMS (ESI+) 544 ($M+Na^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 544.1206; $[C_{25}H_{31}NNaO_5Se]^+$ requires 544.1209.

Di-tert-*butyl 2-(*N-*(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate* S19



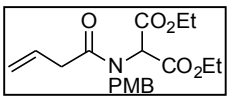
Prepared from 4-(phenylselanyl)butanoic acid **18** (2.48 g, 10.2 mmol) and aminomalonate **22** (2.99 g, 8.51 mmol) using General Procedure D and purified by flash column chromatography (2:1 petroleum ether 40–60 °C:diethyl ether), which gave *di*-tert-*butyl 2-(*N-*(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate* **S19** as a colourless oil (3.96 g, 5.13 mmol, 60%); R_f = 0.70 (1:1 petroleum ether 40–60 °C:diethyl ether); ν_{max} (thin film) 2978s (C-H), 2934s (C-H), 1733m (C=O ester), 1661s (C=O amide), 1215s, 1144s; δ_H (500 MHz, $CDCl_3$) 1.38 (18H, s, C(CH_3)$_3$), 2.03 (2H, tt, *J* = 7.3, 7.3, SeCH_2CH_2), 2.45 (2H, t, *J* = 7.3, SeCH_2), 2.91 (2H, t, *J* = 7.3, CH_2C(O)), 3.80 (3H, s, OCH_3), 4.64 (2H, s, ArCH_2), 5.36 (1H, s, C*H*(CO_2*t*Bu)$_2$), 6.87–7.43 (9H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 25.6 (*C*H_3), 27.9 (*C*H_2), 28.1 (*C*H_2), 33.0 (*C*H_2), 50.2 (*C*H_2), 55.5 (*C*H_3), 62.9 (*C*H), 82.9 (*C*), 114.2 (*C*H), 126.9 (*C*H), 127.6 (*C*H), 129.2 (*C*H), 129.8 (*C*H), 130.2 (*C*), 132.6 (*C*), 159.1 (*C*), 165.6 (*C*(O)), 173.8 (*C*(O)); LRMS (ESI+) 600 ($[M+Na]^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 600.1831; $[C_{29}H_{39}NNaO_6Se]^+$ requires 600.1837.

*Dimethyl 2-(*N-*(4-methoxybenzyl)but-3-enamido)malonate* 11a



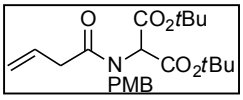
Prepared from dimethyl 2-(*N*-(4-methoxybenzyl)-4-(phenylselanyl)butanamido malonate **S17** (369 mg, 0.750 mmol) using General Procedure E and purified by flash column chromatography (3:1 petroleum ether 40–60 °C:ethyl acetate), which gave *dimethyl 2-(*N-*(4-methoxylbenzyl)but-3-enamido)malonate* **11a** as a pale yellow oil (115 mg, 0.343 mmol, 46%); R_f 0.32 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2955w (C-H), 1744s (ester C=O), 1661s (amide C=O); δ_H (500 MHz, $CDCl_3$) 3.21 (2H, dt, *J* = 6.5, 1.4, CH_2C(O)), 3.66 (6H, s, (CO_2CH_3)$_2$), 3.81 (3H, s, ArOCH_3), 4.65 (2H, s, ArCH_2), 5.13–5.22 (2H, m, CH=CH_2), 5.37 (1H, s, C*H*(CO_2Me)$_2$), 5.97 (1H, ddt, *J* = 16.8, 10.3, 6.5), 6.89 (2H, d, *J* = 8.7, Ar*H*), 7.17 (2H, d, *J* = 8.7, Ar*H*); δ_C (126 MHz, $CDCl_3$) 38.6 (*C*H_2), 50.8 (*C*H_2), 53.0 (*C*H_3), 55.4 (*C*H_3), 60.8 (*C*H), 114.3 (*C*H), 118.5 (*C*H_2), 127.9 (*C*H), 130.9 (*C*H), 159.3 (*C*), 166.7, (*C*=O) 172.5 (*C*=O); LRMS (ESI+) 358 ($[M+Na]^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 358.1251; $[C_{17}H_{21}NNaO_6]^+$ requires 358.1261.

*Diethyl 2-(*N-*(4-methoxybenzyl)but-3-enamido)malonate* 11b



Prepared from diethyl 2-(*N*-(4-methoxybenzyl)-4-(phenylselanyl)butanamido malonate **S18** (654 mg, 1.26 mmol) using General Procedure E and purified by flash column chromatography (4:1 petroleum ether 40–60 °C:ethyl acetate), which gave *diethyl 2-(*N-*(4-methoxylbenzyl)but-3-enamido)malonate* **11b** as a pale yellow oil (215 mg, 0.592 mmol, 47%); R_f 0.37 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2983w (C-H), 1738s (ester C=O), 1662s (amide C=O); δ_H (500 MHz, $CDCl_3$) 1.22 (6H, t, *J* = 7.2, (CO_2CH_2CH_3)$_2$), 3.19 (2H, dt, *J* = 6.3, 1.5, CH_2C(O)), 3.81 (3H, s, OCH_3), 4.06 (2H, dq, *J* = 10.8, 7.2, (CO_2C*H*H'CH_3)$_2$), 4.16 (2H, dq, *J* = 10.8, 7.2, (CO_2CH*H'*CH_3)$_2$), 4.66 (2H, s, ArCH_2), 5.12–5.21 (2H, m, H_2C=CH), 5.40 (1H, s, C*H*(CO_2Et)$_2$), 5.96 (1H, ddt, *J* = 16.5, 10.2, 6.3, CH_2C=C*H*), 6.88 (2H, d, *J* = 8.7, Ar*H*), 7.18 (2H, d, *J* = 8.7, Ar*H*); δ_C (126 MHz, $CDCl_3$) 14.0 (*C*H_3), 38.6 (*C*H_2), 50.6 (*C*H_2), 55.5 (*C*H_3), 61.1 (*C*H), 62.2 (*C*H_2), 114.2 (*C*H), 118.4 (*C*H_2), 127.9 (*C*H), 128.3 (*C*), 131.0 (*C*H), 159.2 (*C*), 166.4 (*C*(O)), 172.6 (*C*(O)); LRMS (ESI+) 386 ($[M+Na]^+$, 100%); HRMS (ESI+) found $[M+Na]^+$ 386.1564; $[C_{19}H_{25}NNaO_6]^+$ requires 386.1574.

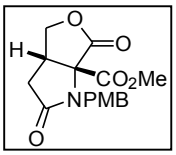
Following General Procedure E *for the synthesis of* ***11a*** *and* ***11b****, significant inclusion of phenylselenium at the malonate position occurred, co-eluting in all solvent systems in both cases. Unoptimised oxidation of the mixture with 5 eq. $NaIO_4$ and $NaHCO_3$ in 1:1:1 MeOH/THF/H_2O (0.10 M) for 30 min, followed by direct purification by flash column chromatography allowed separation of the mixture, and the yield quoted is over these two steps.This did not occur with* tert-*butyl malonates.*



Di-tert-*butyl 2-(N-(4-methoxybenzyl)but-3-enamido)malonate* 11c

Prepared from di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate **S19** (1.31 g, 2.27 mmol) using General Procedure E and purified by flash column chromatography (6:1 petroleum ether 40–60 °C:ethyl acetate), which gave *di*-tert-*butyl 2-(*N-*(4-methoxybenzyl)but-3-enamido)malonate* **11c** as a colourless oil (0.794 g, 1.89 mmol, 83%); R_f = 0.61 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2979s (C-H), 1732s (C=O ester), 1665s (C=O amide); δ_H (500 MHz, $CDCl_3$) 1.38 (18H, s, C(CH_3)$_3$), 3.11 (2H, d, *J* = 6.5, CH_2C(O)), 3.79 (3H, s, OCH_3), 4.68 (2H, s, ArCH_2), 5.09 (1H, dd, *J* = 17.2, 1.5, CH_EH_Z=CH), 5.14 (1H, dd, *J* = 10.4, 1.5, CH_EH_Z=CH), 5.42 (1H, s, C*H*($CO_2{}^tBu$)$_2$), 5.94 (1H, ddt, *J* = 17.2, 10.4, 6.5, CH_2=C*H*), 6.87 (2H, d, *J* = 8.6, Ar*H*), 7.17 (2H, d, *J* = 8.6, Ar*H*); δ_C (126 MHz, $CDCl_3$) 27.9 (*C*H_3), 38.7 (*C*H_2), 50.1 (*C*H_2), 55.5 (*C*H_3), 62.6 (*C*H), 82.9 (*C*), 114.2 (*C*H), 118.2 (*C*H_2), 127.5 (*C*H), 129.1 (*C*H), 131.2 (*C*), 159.1 (*C*), 165.6 (*C*(O)), 172.7 (*C*(O)); LRMS (ESI+) 442 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 442.2184; [$C_{23}H_{33}NNaO_6$]$^+$ requires 442.2200.

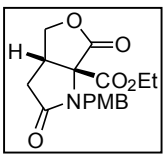
(3aS,6aS*)-Methyl 1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* 12a



Prepared from dimethyl 2-(*N*-(4-methoxybenzyl)but-3-enamido)malonate **11a** (50.0 mg, 0.150 mmol) using General Procedure F and purified by flash column chromatography (1:1→0:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3aS*,6aS*)-methyl 1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* **12a** as a colourless gum (36.1 mg, 0.113 mmol, 75%); R_f 0.28 (ethyl acetate); ν_{max} (thin film) 2957w (C-H), 1780s (lactone C=O), 1753m (ester C=O), 1704s (lactam C=O); δ_H (500 MHz, $CDCl_3$) 2.40 (1H, dd, *J* = 17.5, 1.5, C*H*HC(O)), 2.78 (1H, dd, *J* = 17.5, 8.3, C*H*HC(O)), 3.36 (1H, dddd, *J* = 8.5, 8.3, 7.8, 1.7, CH_2C*H*), 3.67 (3H, s, CO_2CH_3), 3.77 (3H, s, ArOCH_3), 3.96 (1H, dd, *J* = 9.5, 7.8, C*H*HO), 4.51 (1H, d, *J* = 15.1, ArC*H*H), 4.64 (1H, dd, *J* = 9.5, 8.5, CH*H*O), 4.69 (1H, d, *J* = 15.1, ArCH*H*), 6.81 (2H, d, *J* = 8.8, Ar*H*), 7.26 (2H, d, *J* = 8.8, Ar*H*); δ_C (126 MHz, $CDCl_3$) 34.1 (*C*H_2), 39.2 (*C*H), 45.1 (*C*H_2), 53.6 (*C*H_3), 55.3 (*C*H_3), 70.7 (*C*), 71.5 (*C*H_2), 113.8 (*C*H), 128.2 (*C*), 130.3 (*C*H), 159.1 (*C*), 168.0 (*C*(O)), 169.1 (*C*(O)), 173.0 (*C*(O)); LRMS (ESI+) 342 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 342.0947, [$C_{16}H_{17}NNaO_6$]$^+$ requires 342.0948.

Relative configuration assigned by analogy with other [3.3.0]-bicylic lactones prepared in this paper.

(3aS,6aS*)-Ethyl 1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* 12b

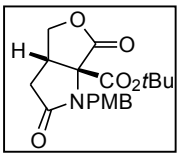


Prepared from diethyl 2-(*N*-(4-methoxybenzyl)but-3-enamido)malonate **11b** (73.0 mg, 0.200 mmol) using General Procedure F and purified by flash column chromatography (2% *iso*-propanol in chloroform), which gave *(3a*R**,6a*S**)-ethyl 1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* **12b** as a colourless oil

(32.3 mg, 96.7 μmol, 48%); R_f 0.29 (ethyl acetate); ν_{max} (thin film) 2954w (C-H), 1779s (lactone C=O), 1749m (ester C=O), 1706s (lactam C=O); δ_H (500 MHz, $CDCl_3$) 1.23 (3H, t, *J* = 7.2, CH_2CH_3), 2.40 (1H, dd, *J* = 17.5, 1.6, C*H*H'C(O)), 2.77 (1H, dd, *J* = 17.5, 8.2, CH*H*'C(O)), 3.36 (1H, dddd, *J* = 8.6, 8.2, 7.6, 1.6, C*H*CH_2C(O)), 3.77 (3H, s, OCH_3), 3.96 (1H, dd, *J* = 9.4, 7.4, C*H*H'O), 4.08 (1H, dq, *J* = 10.7, 7.2, C*H*H'CH_3), 4.21 (1H, dq, *J* = 10.7, 7.2, CH*H*'CH_3), 4.49 (1H, d, *J* = 15.1, ArC*H*H'), 4.65 (1H, dd, *J* = 9.4, 8.6, CH*H*'O), 4.72 (1H, d, *J* = 15.1, ArCH*H*'), 6.81 (2H, d, *J* = 8.7, Ar*H*), 7.27 (2H, d, *J* = 8.7, Ar*H*); δ_C (126 MHz, $CDCl_3$) 14.0 (CH_3), 34.1 (CH_2), 39.3 (*C*H), 45.2 (CH_2), 55.3 (CH_3), 63.2 (CH_3), 70.8 (*C*), 71.5 (CH_2), 113.8 (*C*H), 128.3 (*C*), 130.3 (*C*H), 159.1 (*C*), 167.6 (*C*(O)), 169.3 (*C*(O)), 173.1 (*C*(O)); LRMS (ESI+) 356 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 356.1093, $[C_{17}H_{19}NNaO_6]^+$ requires 356.1105.

Relative configuration assigned by analogy with other [3.3.0]-bicylic lactones prepared in this paper.

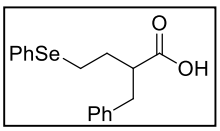
(3aS,6a*R**)*-tert-*Butyl 1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* 12c



Prepared from di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)but-3-enamido)malonate **11c** (126 mg, 0.300 mmol) using General Procedure F and purified by flash column chromatography (3:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3aS*,6a*R**)*-tert-*butyl 1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* **12c** as a colourless oil (80.0 mg, 0.221 mmol, 74%); R_f 0.34 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2979s (C-H), 1782s (lactone C=O), 1741s (ester C=O), 1710s (lactam C=O); δ_H (500 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 2.38 (1H, dd, *J* = 17.5, 1.8, C*H*H'C(O)), 2.76 (1H, dd, *J* = 17.5, 8.3, CH*H*'C(O)), 3.32 (1H, dddd, *J* = 8.5, 8.3, 7.6, 1.8, C*H*CH_2O), 3.78 (3H, s, OCH_3), 3.94 (1H, dd, *J* = 9.4, 7.6, C*H*H'O), 4.47 (1H, d, *J* = 15.1, ArC*H*H'), 4.63 (1H, dd, *J* = 9.4, 8.5, CH*H*'O), 4.72 (1H, d, *J* = 15.1, ArCH*H*'), 6.81 (2H, d, *J* = 8.7, Ar*H*), 7.28 (2H, d, *J* = 8.7, Ar*H*); δ_C (126 MHz, $CDCl_3$) 27.9 (CH_3), 34.1 (CH_2), 39.5 (*C*H), 45.4 (CH_2), 55.3 (CH_3), 71.4 (CH_2), 85.0 (*C*), 113.9 (*C*H), 128.6 (*C*), 130.3 (*C*H), 159.1 (*C*), 166.5 (*C*(O)), 169.7 (*C*(O)), 173.2 (*C*(O)); LRMS (ESI+) 384 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 384.1411, $[C_{19}H_{23}NNaO_6]^+$ requires 384.1418.

Relative configuration assigned by analogy with other [3.3.0]-bicylic lactones prepared in this paper.

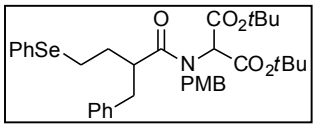
2-Benzyl-4-(phenylselanyl)butanoic acid S20



To a stirred solution of diphenyl diselenide (936 mg, 3.00 mmol) in dry, N_2 sparged DMF (20 mL) was added $NaBH_4$ (336 mg, 7.00 mmol) portionwise (*caution! gas evolution*). The solution was heated to 100 °C for 30 mins and then a solution of 3-benzyldihydrofuran-2(3*H*)-one **S9** (881 mg, 5.00 mmol) in dry, N_2 sparged DMF (5.0 mL) was added. The solution was stirred at 120 °C for 2 h, and then cooled to RT. The reaction was quenched by the addition of 2 M aqueous NaOH solution (20 mL), and diluted with Et_2O (20 mL). The layers were separated, and the organic layer was extracted with 2 m aqueous NaOH solution (2×15 mL). The combined aqueous extracts were acidified to pH 2 with conc. HCl. The aqueous phase was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (8:1 petroleum ether 40–60 °C:ethyl acetate), which gave *2-benzyl-4-(phenylselanyl)butanoic acid* **S20** as a colourless oil (1.25 g 3.75 mmol, 75%); R_f = 0.40 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3060m (C-H), 2930w br (O-H),

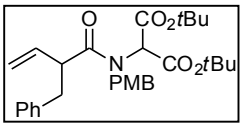
1702 (C=O); ^{1}H (400 MHz, $CDCl_3$) 1.87 (1H, dddd, *J* = 14.2, 9.3, 6.8, 4.7, $SeCH_2CHH'$), 2.07 (1H, dddd, *J* = 14.2, 9.0, 9.0, 5.5, $SeCH_2CHH'$), 2.75 (1H, dd, *J* = 13.4, 7.2, $PhCHH'$), 2.81–2.88 (1H, m, $SeCHH'$), 2.88–2.93 (1H, m, CHC(O)), 2.93–2.99 (1H, m, $SeCHH'$), 3.03 (1H, dd, *J* = 13.4, 7.3, $PhCHH'$), 7.15–7.17 (2H, m, Ar*H*), 7.21–7.31 (6H, m, Ar*H*), 7.42–7.44 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_2), 31.7 (CH_2), 37.9 (CH_2), 47.1 (CH), 126.7 (CH), 127.1 (CH), 128.7 (CH), 129.0 (CH), 129.2 (CH), 129.7 (CH), 133.0 (*C*), 138.6 (*C*), 181.0 (C(O)); LRMS (ESI–) 333 ([M-H]$^-$, 100%); HRMS (ESI–) found [M–H]$^-$ 333.0408; $[C_{17}H_{17}O_2Se]^-$ requires 333.0400.

Di-tert-*butyl 2-(2-benzyl*-N-*(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate* **S21**



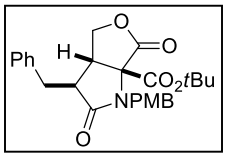
Prepared from 2-benzyl-4-(phenylselanyl)butanoic acid **S20** (1.33 g, 4.00 mmol) and aminomalonate **22** using General Procedure D and purified by flash column chromatography (8:1 petroleum ether 40–60 °C:ethyl acetate), which gave *di*-tert-*butyl 2-(2-benzyl*-N-*(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate* **S21** as a colourless oil (2.11 g 3.16 mmol, 79%); R_f = 0.61 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2977s (C-H), 1732s (C=O ester), 1656s (C=O amide); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, $CH(CO_2C(CH_3)_3)(CO_2C(CH'_3)_3)$), 1.44 (9H, s, $CH(CO_2C(CH_3)_3)(CO_2C(CH'_3)_3)$), 1.65–1.77 (1H, m, $SeCH_2CHH'$), 2.08–2.18 (1H, m, $SeCH_2CHH'$), 2.57 (1H, dd, *J* = 13.2, 7.8, $PhCHH'$), 2.75 (1H, ddd, *J* = 12.1, 7.7, 7.7, $SeCHH'$), 3.10–2.90 (3H, m, $SeCHH'$, $PhCHH'$, CHC(O)), 3.80 (3H, s, OCH_3), 4.50 (1H, d, *J* = 17.5, $ArCHH'$), 4.77 (1H, d, *J* = 17.5, $ArCHH'$), 5.28 (1H, s, $CH(CO_2tBu)_2$), 6.81–6.85 (4H, m, Ar*H*), 7.07 (2H, d, *J* = 8.1, Ar*H*), 7.14–7.21 (6H, m, Ar*H*), 7.29–7.34 (2H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 25.4 (CH_2); 27.9 (CH_3), 28.0 (CH_3), 32.5 (CH_2), 38.6 (CH_2), 43.9 (CH), 50.3 (CH_2), 55.5 (CH_3), 63.5 (CH), 82.9 (*C*), 114.3 (CH), 126.4 (CH), 126.9 (CH), 127.8 (CH), 128.5 (CH), 129.1 (CH), 129.4 (CH), 129.4 (CH), 129.9 (CH), 132.8 (*C*), 139.3 (*C*), 159.1 (*C*), 165.5 (C(O)), 176.7 (C(O)); LRMS (ESI+) 690 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 690.2275; $[C_{36}H_{45}NNaO_6Se]^+$ requires 690.2307.

Di-tert-*butyl 2-(2-benzyl*-N-*(4-methoxybenzyl)but-3-enamido)malonate* **11d**



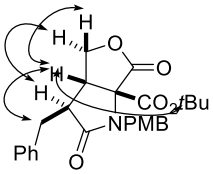
Prepared from di-*tert*-butyl 2-(2-benzyl-*N*-(4-methoxybenzyl)-4-(phenylselanyl)butanamido)malonate **S21** (273 mg, 0.409 mmol) using General Procedure E and purified by flash column chromatography (8:1 petroleum ether 40–60 °C:ethyl acetate), which gave *di*-tert-*butyl 2-(2-benzyl*-N-*(4-methoxybenzyl)but-3-enamido)malonate* **11d** as a colourless oil (204 mg, 0.400 mmol, 98%); R_f = 0.61 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3978m (C-H), 1732s (C=O ester), 1660s (C=O amide); δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, $CH(CO_2C(CH_3)_3)(CO_2C(CH'_3)_3)$), 1.42 (9H, s $CH(CO_2C(CH_3)_3)(CO_2C(CH'_3)_3)$), 2.74 (1H, dd, *J* = 13.4, 6.6, $PhCHH'$), 3.17 (1H, dd, *J* = 13.4, 7.6, $PhCHH'$), 3.40 (1H, ddd, *J* = 7.9, 7.6, 6.6, CHC(O)), 3.79 (3H, s, OCH_3), 4.47 (1H, d, *J* = 17.7, $ArCHH'$), 4.71 (1H, d, *J* = 17.7, $ArCHH'$), 5.00 (1H, d, *J* = 17.5, $HH'C=CH$), 5.11 (1H, d, *J* = 10.4, $HH'C=CH$), 5.37 (1H, s, $CH(CO_2tBu)_2$), 5.84 (1H, ddd, *J* = 17.5, 10.4, 7.7, $H_2C=CH$), 6.66–6.77 (2H, m, Ar*H*), 6.93 (2H, d, *J* = 8.8, Ar*H*), 7.02 (2H, d, *J* = 8.8, Ar*H*), 7.18–7.24 (3H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 27.7 (CH_3), 28.0 (CH_3), 39.1 (CH_2), 49.6 (CH), 49.9 (CH_2), 55.5 (CH_3), 62.9 (CH), 82.8 (*C*), 82.9 (*C*), 114.1 (CH), 117.6 (CH_2), 126.3 (CH), 127.4 (CH), 128.4 (CH), 129.3 (CH), 129.6 (CH), 136.2 (CH), 139.3 (*C*), 158.9 (*C*), 165.4 (C(O)), 165.7 (C(O)), 174.5 (C(O)); LRMS (ESI+) 532 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 532.2673; $[C_{30}H_{39}NNaO_6]^+$ requires 532.2670.

(3S,3aS*,6a*R**)*-tert-*Butyl 3-benzyl-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-b]pyrrole-6a-carboxylate* 12d

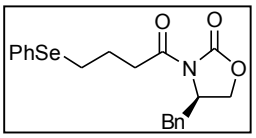


Prepared from di-*tert*-butyl 2-(2-benzyl-*N*-(4-methoxybenzyl)but-3-enamido)malonate **11d** (153 mg, 0.300 mmol) according to General Procedure F and purified by flash column chromatography (4:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3*S**,3a*S**,6a*R**)*-tert-*butyl 3-benzyl-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H-*furo[3,4-*b*]pyrrole-6a-carboxylate* **12d** as a colourless oil (66.4 mg, 0.147 mmol, 49%); R_f = 0.12 (1:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max}/cm^{-1} 2979m (C-H), 1783s (C=O γ-lactone), 1738m (C=O ester), 1708s (C=O γ-lactam), 1513s, 1248s, 1152s; δ_H (500 MHz, $CDCl_3$) 1.46 (9H, s, C(C*H*$_3$)$_3$), 2.64 (1H, dd, *J* = 13.9, 11.4, PhCH*H*'), 2.75 (1H, ddd, *J* = 11.4, 4.0, 3.4, C*H*C(O)), 3.09 (1H, ddd, *J* = 8.3, 6.1, 3.4, C*H*CH$_2$O), 3.38 (1H, dd, *J* = 13.9, 4.0, PhC*H*H'), 3.78 (1H, dd, *J* = 9.5, 6.1, C*H*$_\beta$H$_\alpha$O), 3.78 (3H, s, OC*H*$_3$), 4.36 (1H, dd, *J* = 9.5, 8.3, CH$_\beta$*H*$_\alpha$O), 4.50 (1H, d, *J* = 15.3, ArCH*H*'), 4.80 (1H, d, *J* = 15.3, ArC*H*H'), 6.83 (2H, d, *J* = 8.5, Ar*H*), 7.15 (2H, d, *J* = 8.5, Ar*H*), 7.26–7.35 (5H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 27.9 (*C*H$_3$), 36.4 (*C*H$_2$), 44.1 (*C*H), 45.8 (*C*H$_2$)), 48.6 (*C*H), 55.3 (*C*H$_3$), 70.6 (*C*), 71.0 (*C*H$_2$), 85.1 (*C*), 113.8 (*C*H), 127.2 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 129.1 (*C*H), 130.1 (*C*), 137.8 (*C*), 158.1 (*C*), 166.9 (*C*(O)), 170.1 (*C*(O)), 174.9 (*C*(O)); LRMS (ESI+) 474 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 474.1881; [$C_{26}H_{29}NNaO_6$]$^+$ requires 474.1887.

Key nOe data:

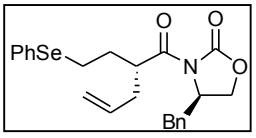


*(*R*)-4-Benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one* 20



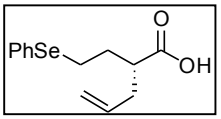
To a stirred solution of 4-(phenylselanyl)butanoic acid **18**[6] (2.43 g, 10.0 mmol) in dry THF (80 mL) at -10 °C was added triethylamine (3.70 mL, 27.0 mmol) and pivaloyl chloride (1.35 mL, 11.0 mmol). The reaction was stirred for at -10 °C for 1 h, then LiCl (466 mg, 11.0 mmol) and (*R*)-4-benzyloxazolidin-2-one (1.95 g, 11.0 mmol) were added. The solution was warmed to RT overnight, then diluted with EtOAc (50 mL) and washed successively with sat. aq. $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (3:1 petroleum ether 40-60 °C:ethyl acetate), which gave *(*R*)-4-benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one* **20** as a white solid (3.70 g, 9.20 mmol, 92%); m.p. 36—39 °C; R_f 0.37 (3:1 petroleum ether 40-60 °C:ethyl acetate); ν_{max} (thin film) 1780s (C=O imide), 1699m (C=O amide); δ_H (500 MHz, $CDCl_3$) 2.11 (2H, tt, *J* = 7.2, 7.2, PhSeCH$_2$C*H*$_2$), 2.75 (1H, dd, *J* = 13.4, 10.0, PhC*H*H'), 3.01 (2H, t, *J* = 7.2, PhSeC*H*$_2$), 3.09 (2H, t, *J* = 7.2, PhSeCH$_2$CH$_2$C*H*$_2$), 3.28 (1H, dd, *J* = 13.4, 3.3, PhCH*H'*), 4.16 (1H, dd, *J* = 14.6, 3.3, C(O)OC*H*H'), 4.19 (1H, dd, *J* = 14.6, 6.4, C(O)CH*H'*), 4.64 (1H, dddd, *J* = 10.0, 6.4, 3.3, 3.3, C(O)NC*H*), 7.20 (2H, d, *J* = 7.1 Hz, Ar*H*), 7.22–7.31 (4H, m, Ar*H*), 7.34 (2H, t, *J* = 7.2, Ar*H*), 7.53 (2H, dd, *J* = 7.8, 1.4, Ar*H*); δ_C (126 MHz, $CDCl_3$) 24.8 (*C*H$_2$), 27.1 (*C*H$_2$), 35.4 (*C*H$_2$), 38.1 (*C*H$_2$), 55.2 (*C*H), 66.4 (*C*H$_2$), 127.0 (*C*H), 127.5 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.5 (*C*H), 130.1 (*C*), 132.9 (*C*H), 135.4 (*C*), 153.5 (*C*(O)), 172.5 (*C*(O)); *m/z* LRMS (ESI+) 426 (M+Na$^+$, 100%), 829 (2M+Na$^+$, 29%); HRMS found [M+Na]$^+$ 426.0593; [$C_{20}H_{21}NNaO_3Se$]$^+$ requires 426.0579; $[\alpha]_D$ (25 °C) −39.1 (c = 1.03 in $CHCl_3$).

*(*R*)-4-Benzyl-3-((*R*)-2-(2-(phenylselanyl)ethyl)pent-4-enoyl)oxazolidin-2-one* **21**



To a stirred solution of NaHMDS (2 M in THF, 5.00 mL, 10.0 mmol) at -78 °C was added dropwise a solution of (*R*)-4-benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one **20** (3.44 g, 8.56 mmol) in dry THF (8.5 mL), maintaining an internal temperature <70 °C. After stirring for 30 min, allyl iodide (filtered through neutral alumina immediately prior to use) (2.35 mL, 25.7 mmol) was added dropwise maintaining an internal temperature <70 °C and the solution was stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl solution (22 mL) and then diluted with ethyl acetate (100 mL). The layers were separated and the organic phase was washed successively with water (20 mL), 1 M aq. $NaHCO_3$ solution (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography (6:1 petroleum ether 40-60 °C:ethyl acetate), which gave *(*R*)-4-benzyl-3-((*R*)-2-(2-(phenylselanyl)ethyl)pent-4-enoyl)oxazolidin-2-one* **21** as a colourless oil (3.13 g, 7.06 mmol, 82%); R_f 0.24 (6:1 petroleum ether 40-60 °C:ethyl acetate); ν_{max} (thin film) 2920w (C-H), 1777s (C=O imide), 1695s (C=O amide); δ_H (500 MHz, $CDCl_3$) 1.89 (1H, dddd, *J* = 14.2, 9.3, 6.6, 4.9, $PhSeCH_2CHH$), 2.21 (1H, dddd, *J* = 14.2, 8.9, 8.9, 5.6 Hz, $PhSeCH_2CHH$), 2.32 (1H, ddd, *J* = 13.9, 7.1, 6.7, $H_2C=CHCHH$), 2.47 (1H, ddd, *J* = 13.9, 7.1, 7.0, $H_2C=CHCHH$), 2.66 (1H, dd, *J* = 13.3, 10.0, PhC*H*H), 2.87 (1H, ddd, *J* = 12.2, 9.0, 6.6, PhSeC*H*H), 2.96 (1H, ddd, *J* = 12.2, 9.2, 5.5, PhSeCH*H*), 3.28 (1H, dd, *J* = 13.3, 3.3, PhCH*H*), 4.03 (1H, dddd, *J* = 8.9, 7.0, 6.7, 4.9, C*H*C(O)), 4.09–4.17 (2H, m, $NCHCH_2$), 4.59–4.68 (1H, m, NC*H*), 5.03–5.08 (1H, m, *H*H'C=CH), 5.08 (1H, d, *J* = 17.1, H*H'*C=CH), 5.79 (1H, dddd, *J* = 17.1, 10.1, 7.1, 7.1, $H_2C=CH$), 7.20–7.31 (6H, m, Ar*H*), 7.34 (2H, t, *J* = 7.3, Ar*H*), 7.49 (2H, dd, *J* = 8.0, 1.6, Ar*H*); δ_C (126 MHz, $CDCl_3$) 25.3 (CH_2), 31.7 (CH_2), 36.8 (CH_2), 38.2 (CH_2), 42.6 (*C*H), 55.6 (*C*H), 66.1 (CH_2), 117.8 (CH_2), 127.0 (*C*H), 127.5 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.5 (*C*H), 130.1 (*C*), 132.8 (*C*H), 134.8 (*C*H), 135.4 (*C*), 153.2 (*C*(O)), 175.1 (*C*(O)); *m/z* LRMS (ESI+) 466 ($M+Na^+$, 100%), 909 ($2M+Na^+$, 29%); HRMS found $[M+Na]^+$ 466.0896; $[C_{23}H_{25}NNaO_3Se]^+$ requires 466.0892; $[\alpha]_D$ (25 °C) −46.5 (c = 1.19 in $CHCl_3$).

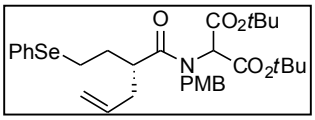
*(*R*)-2-(2-(Phenylselanyl)ethyl)pent-4-enoic acid* **S22**



To a stirred solution of BnOH (0.50 mL, 4.70 mmol) in dry, N_2 sparged THF (15.0 mL) was added *n*BuLi (1.6 M in hexanes, 2.35 mL, 3.75 mmol) dropwise at 0 °C. The solution was stirred for 30 min and then cooled to -55 °C. A solution of (*R*)-4-benzyl-3-((*R*)-2-(2-(phenylselanyl)ethyl)pent-4-enoyl)oxazolidin-2-one **21** (1.45 g, 3.27 mmol) in dry, N_2 sparged THF (15 mL) was then added dropwise. The reaction was allowed to warm slowly to -35 °C and stirred at this temperature for 30 min. After warming to 0 °C and stirring for a further 20 min, 0.5 M LiOH solution (1:1 methanol:water, 32 mL, 15.7 mmol). The solution was stirred overnight at RT and then 0.5 M aqueous NaOH solution (20 mL) was added. The THF and methanol were removed *in vacuo* and residue was diluted with dichloromethane (20 mL). The layers were separated and the organic phase was extracted with 0.5 M aqueous NaOH solution (2×20 mL). The combined aqueous extracts were carefully acidifed to pH 2 with conc. HCl, and extracted with diethyl ether (3×20 mL). The combined organic extracts were dried which gave *(*R*)-2-(2-(phenylselanyl)ethyl)pent-4-enoic acid* **S22** as a colourless oil (873 mg, 3.07 mmol, 94%); R_f = 0.17 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 3073m (O-H), 2933mbr (C-H), 1701s (C=O carboxylic acid); δ_H (400 MHz, $CDCl_3$) 1.82–1.96 (1H, m, $SeCH_2CHH'$), 2.08 (1H, dddd, *J* = 14.4, 8.9, 8.9, 5.7, $SeCH_2CHH'$), 2.20–2.34 (1H, m, $H_2C=CHCHH'$), 2.42 (1H, ddd, *J* = 14.3, 7.1, 7.1, $H_2C=CHCHH'$), 2.67 (1H, dddd, *J* = 7.1, 7.0, 6.8, 6.8, C*H*C(O)), 2.90 (1H, ddd, *J* = 12.3, 9.1, 6.7, SeC*H*H'), 2.99 (1H, ddd, *J* = 12.3, 9.4, 5.7, SeCH*H'*), 5.06 (1H, d, *J* = 10.1, *H*H'C=CH), 5.09 (1H, d, *J* = 17.1, H*H'*C=CH), 5.73 (1H, ddt,

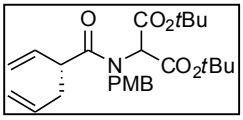
J = 17.1, 10.1, 7.0, CH_2=C*H*), 7.25–7.30 (3H, m, Ar*H*), 7.49–7.52 (2H, m, Ar*H*); δ_C NMR (100 MHz, $CDCl_3$) 25.1 (Se*C*H_2), 31.6 (*C*H_2), 35.9 (*C*H_2), 45.0 (*C*H), 117.7 (*C*H_2), 127.1 (*C*H), 129.2 (*C*H), 129.9 (*C*H), 132.8 (*C*), 134.7 (*C*H), 181.2 (*C*(O)); LRMS (ESI+) 307 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+H]$^+$ 283.0245; [$C_{13}H_{15}O_2Se$]$^+$ requires 283.0243; $[\alpha]_D$ (25 °C) −33.8 (c = 0.50 in CH_2Cl_2).

*(*R*)-Di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)-2-(2-(phenylselanyl)ethyl)pent-4-enamido)malonate* 23



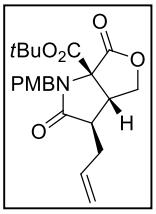
To a stirred solution of (*R*)-2-(2-(phenylselanyl)ethyl)pent-4-enoic acid **S22** (619 mg, 2.18 mmol) in dry DCM (5.6 mL) with a drop of DMF was added oxalyl chloride (171 µL, 2.0 mmol) dropwise. The solution was stirred for 1 h, and then rapidly transferred to a vigorously stirred solution of di-*tert*-butyl 2-(4-methoxybenzylamino)malonate **22**(547 mg, 1.56 mmol) in 1:1 DCM:sat. aq. $NaHCO_3$ solution (5.6 mL). The solution was stirred for 16 h, and then filtered through a plug of silica, eluting with 1:1 petrol ether 40–60 °C:diethyl ether. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (10% ethyl acetate in DCM), which gave *(*R*)-di-tert-butyl 2-(*N*-(4-methoxybenzyl)-2-(2-(phenylselanyl)ethyl)pent-4-enamido)malonate* **23** as a colourless oil (575 mg, 0.936 mmol, 60%); R_f = 0.57 (3:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2978s (C-H), 1732s (C=O ester), 1657s (C=O amide I); δ_H (500 MHz, $CDCl_3$) 1.41 (9H, s CH($CO_2C(CH_3)_3$)($CO_2C(CH'_3)_3$)), 1.41 (9H, m, CH($CO_2C(CH_3)_3$)($CO_2C(CH'_3)_3$)), 1.78 (1H, dddd, *J* = 12.0, 8.8, 6.9, 5.4, $SeCH_2CH$*H*'), 2.08–2.16 (2H, m, CH_2=CHC*H*H', $SeCH_2CH$H'), 2.33 (1H, m, CH_2=CHC*H*H'), 2.72–2.82 (2H, m, SeC*H*H', C*H*C(O)), 2.94 (1H, ddd, *J* = 12.0, 8.5, 5.7, SeC*H*H'), 3.79 (3H, s, OCH_3), 4.62 (1H, d, *J* = 17.4, ArCH*H*'), 4.73 (1H, d, *J* = 17.4, ArC*H*H'), 4.92–4.97 (2H, m, CH_2=CH), 5.16 (1H, s, C*H*(CO_2tBu)$_2$), 5.60 (1H, m, CH_2=C*H*), 6.86 (2H, d, *J* = 8.5, Ar*H*), 7.20–7.28 (5H, m, Ar*H*), 7.42–7.43 (2H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$) 25.2 (*C*H_2), 28.0 (*C*H_3), 32.6 (*C*H_2), 36.9 (*C*H_2), 41.7 (*C*H), 50.5 (*C*H_2), 55.5 (*C*H_3), 63.5 (*C*H), 82.8 (*C*), 82.8 (*C*), 114.2 (*C*H), 117.2 (*C*H_2), 126.8 (*C*H), 128.0 (*C*H), 129.1 (*C*H), 129.3 (*C*H), 130.3 (*C*), 132.4 (*C*), 135.5 (*C*H), 159.2 (*C*), 165.5 (*C*(O)), 176.3 (*C*(O)); LRMS (ESI+) 640 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 640.2126; [$C_{32}H_{43}NNaO_6Se$]$^+$ requires 640.2148; $[\alpha]_D$ (25 °C) −10.8 (c = 0.49 in CH_2Cl_2).

*(*R*)-Di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)-2-vinylpent-4-enamido)malonate* (–)-11e



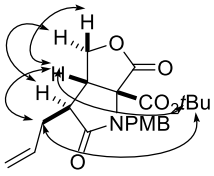
Prepared from (*R*)-di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)-2-(2-(phenylselanyl)ethyl)pent-4-enamido)malonate **23** (306 mg, 0.50 mmol) using General Procedure E and purified by flash column chromatography (5:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(*R*)-di-tert-butyl 2-(*N*-(4-methoxybenzyl)-2-vinylpent-4-enamido)malonate* **(–)-11e** as a colourless oil (183 mg 0.40 mmol, 80%); R_f = 0.40 (5:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2977m (C-H), 1747, 1720s (C=O ester), 1656 (C=O amide I); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s CH($CO_2C(CH_3)_3$)($CO_2C(CH'_3)_3$)), 1.41 (9H, s CH($CO_2C(CH_3)_3$)($CO_2C(CH'_3)_3$)), 2.20–2.29 (1H, m, CH_2=CHCH*H*'), 2.52–2.62 (1H, m, CH_2=CHC*H*H'), 3.18–3.25 (1H, m, C*H*C(O)), 3.80 (3H, s, OCH_3), 4.60 (1H, d, *J* = 17.7, ArCH*H*'), 4.74 (1H, d, *J* = 17.7, ArC*H*H'), 5.00–5.14 (4H, m, CH_2=CHCH, CH_2=$CHCH_2$), 5.29 (1H, s, C*H*(CO_2tBu)$_2$), 5.71 (1H, dddd, *J* = 17.3, 10.1, 7.3, 6.6, CH_2=C*H*CH_2), 5.82 (1H, ddd, *J* = 17.3, 10.1, 7.9, CH_2=C*H*CH), 6.87 (2H, d, *J* = 8.6, Ar*H*), 7.17 (2H, d, *J* = 8.6, Ar*H*); δ_C (126 MHz, $CDCl_3$) 27.7 (*C*H_3), 37.2 (*C*H_2), 47.4 (*C*H), 49.7 (*C*H_2), 55.3 (*C*H_3), 62.9 (*C*H), 82.7 (*C*), 114.0 (*C*H), 116.9 (*C*H_2), 117.2 (*C*H_2), 127.5 (*C*H), 129.1 (*C*H), 135.5 (*C*), 136.3 (*C*H), 159.0 (*C*), 165.4 (*C*(O)), 174.3 (*C*(O)); LRMS (ESI+) 482 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 482.24970; [$C_{26}H_{37}NNaO_6$]$^+$ requires 482.2513; $[\alpha]_D$ (25 °C) −30.2 (c = 0.24 in CH_2Cl_2).

*(3*R*,3a*R*,6aS)*-tert-*Butyl 3-allyl-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-b]pyrrole-6a-carboxylate* (+)-12e

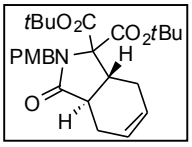


According to modified General Procedure F, alkene **(–)-11e** (69.0 mg, 0.150 mmol) was treated with manganese(III) acetate dihydrate (80.4 mg, 0.300 mmol) and copper(II) triflate (108 mg, 0.300 mmol) and stirred for 1 h. The crude product was purified by flash column chromatography (2:1 petroleum ether 40–60 °C:ethyl acetate), which gave *(3*R*,3a*R*,6a*S*)*-tert-*butyl 3-allyl-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-b]pyrrole-6a-carboxylate* **(+)-12e** as a colourless oil (39.0 mg, 0.0968 mmol, 65%); R_f = 0.32 (2:1 petroleum ether 40–60 °C:ethyl acetate); ν_{max} (thin film) 2979m (C-H), 1781s (C=O γ-lactone), 1736m (C=O ester), 1706 (C=O γ-lactam); δ_H (500 MHz, $CDCl_3$) 1.46 (9H, s, C(CH_3)$_3$), 2.19 (1H, ddd, *J* = 14.2, 9.8, 8.5, CH_2=CHC*H*H'), 2.47 (1H, ddd, *J* = 9.8, 4.2, 3.2, C*H*C(O)), 2.65 (1H, ddd, *J* = 14.2, 5.8, 4.2, CH_2=CHCH*H'*), 3.10 (1H, ddd, *J* = 8.5, 6.6, 3.2, C*H*CH_2O), 3.77 (3H, s, OCH_3), 3.98 (1H, dd, *J* = 8.3, 6.6, C*H*H'O)), 4.45 (1H, d, *J* = 15.2, ArCH*H*'), 4.61 (1H, dd, *J* = 8.5, 8.3, CH*H'*O), 4.80 (1H, d, *J* = 15.2, ArC*H*H'), 5.09 (1H, *J* = 16.8, 1.3, CH*H'*=CH), 5.14 (1H, dd, *J* = 9.8, 1.3, C*H*H'=CH), 5.72 (1H, dddd, *J* = 16.8, 9.8, 8.5, 5.8, CH_2=C*H*CH_2), 6.81 (2H, d, *J* = 8.8, Ar*H*), 7.28 (2H, d, *J* = 8.8, Ar*H*); δ_C (126 MHz, $CDCl_3$) 27.8 (*C*H_3), 34.9 (*C*H_2), 44.0 (*C*H), 46.2 (*C*H), 55.2 (*C*H_3), 70.5 (*C*), 71.2 (*C*H_2), 84.9 (*C*), 113.7 (*C*H), 118.5 (*C*H_2), 128.6 (*C*H), 130.0 (*C*), 134.2 (*C*H), 158.9 (*C*), 166.8 (*C*(O)), 170.1 (*C*(O)), 174.9 (*C*(O)); LRMS (ESI+) 424 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 424.1721; [$C_{22}H_{27}NNaO_6$]$^+$ requires 424.1731; $[\alpha]_D$ (25 °C) +5.7 (c = 0.32 in CH_2Cl_2). Hexahydroisoindolene **(–)-16** (13 mg, 0.0284 mmol, 19%) was also isolated.

Key nOe data:

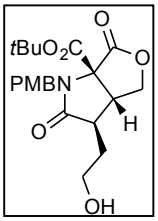


*(3a*R*,7a*R*)-Di-*tert-*butyl 2-(4-methoxybenzyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-1,1-dicarboxylate* (–)-16



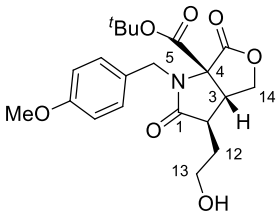
According to modified General Procedure F, alkene **(–)-11e** (69.0 mg, 0.150 mmol) was treated with manganese(III) acetate dihydrate (80.4 mg, 0.300 mmol) and copper(II) triflate (5.4 mg, 0.0150 mmol). The crude product was purified by flash column chromatography (3:1 petroleum ether 40—60 °C:ethyl acetate), which gave *(3a*R*,7a*R*)-di-*tert-*butyl 2-(4-methoxybenzyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-1,1-dicarboxylate* **(–)-16** as colourless crystals (54 mg mg, 0.118 mmol, 79%), m.p. 126—129 °C ($CHCl_3$); R_f = 0.65 (2:1 petrol:ethyl acetate); ν_{max}/cm^{-1} 2977m (C-H), 2928m (C-H), 1719s (C=O ester and γ-lactam); δ_H (500 MHz, $CDCl_3$) 1.20 (9H, s, C(CO_2C(CH_3)$_3$)(CO_2C(C*H*'$_3$)$_3$)), 1.46 (9H, s, C(CO_2C(C*H*$_3$)$_3$)(CO_2C(CH'$_3$)$_3$)), 2.05 (1H, m, CH*H*'CHC(O)), 2.21 (1H, m, CH*H*'CHCHC(O)), 2.34 (1H, ddd, *J* = 13.2, 11.4, 5.4, C*H*CHC(O)), 2.40 (1H, m, C*H*H'CHC(O)), 2.56 (1H, m, C*H*H'CHCHC(O)), 2.72 (1H, ddd, *J* = 13.2, 11.7, 4.7 C*H*C(O)), 3.76 (3H, s, OCH_3), 4.33 (1H, d, *J* = 16.1 ArCH*H*'), 4.95 (1H, d, *J* = 16.1 ArC*H*H'), 5.76 (2H, br s, C*H*=C*H*), 6.80 (2H, d, *J* = 8.6, Ar*H*), 7.07 (2H, d, *J* = 8.6, Ar*H*); δ_C (126 MHz, $CDCl_3$); 27.4 (*C*H_2), 28.2 (*C*H_3), 40.4 (*C*H), 42.8 (*C*H), 45.4 (*C*H_2), 55.5 (*C*H_3), 75.0 (*C*), 83.6 (*C*), 83.8 (*C*), 114.0 (*C*H), 126.4 (*C*H_2), 126.8 (*C*H), 127.7 (*C*), 130.4 (*C*), 158.7 (*C*), 165.6 (*C*(O)), 166.7 (*C*(O)), 177.0 (C(O)); LRMS (ESI+) 480 ([M+Na]$^+$, 100%); HRMS (ESI+) found [M+Na]$^+$ 480.2349; [$C_{26}H_{35}NNaO_6$]$^+$ requires 480.2357; $[\alpha]_D$ (20 °C) -48.0 (c = 1.00 in $CDCl_3$). Lactone **(+)-14e** (6.0 mg, 0.0149 mmol, 10%) was also isolated.

(3*R*,3a*R*,6a*S*)*-tert-*Butyl 3-(2-hydroxyethyl)-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate* 24*[13]



A solution of (3*R*,3a*R*,6a*S*)-*tert*-butyl 3-allyl-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate **(+)-12e** (60.0 mg, 0.149 mmol) in 3:1 DCM:MeOH (10.0 mL) was treated with O_3/O_2 at -78 °C until a pale blue colour persisted. The solution was then purged of O_3 with a stream of O_2 and then treated with a solution of sodium borohydride (7.3 mg, 0.194 mmol) in MeOH (1.0 mL) and stirred for 30 min. The solution was stirred for a further 30 min at 0 °C, and then diluted with ethyl acetate (10 mL). The solution was washed successively with 5% aqueous citric acid solution (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (3:2→1:1 petroleum ether 40-60 °C:ethyl acetate) which gave (3*R*,3a*R*,6a*S*)-*tert*-Butyl 3-(2-hydroxyethyl)-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate **24** (53.1 mg, 0.131 mmol, 88%) as a colourless oil; R_f 0.44 (EtOAc); ν_{max} (thin film) 3400brm (OH), 1782s (γ-lactone C=O), 1743s (ester C=O), 1704s (γ-lactam C=O); δ_H (500 MHz, $CDCl_3$) 1.46 (9H, s, $CO_2C(CH_3)_3$), 1.77 (1H, dddd, *J* = 11.5, 7.3, 7.3, 4.4, $HOCH_2CH$H'CH), 1.99 (1H, dddd, *J* = 11.5, 7.3, 7.3, 4.2, $HOCH_2CH$H'CH), 2.54 (1H, t, *J* = 5.2, OH), 2.61 (1H, ddd, *J* = 7.3, 7.3, 3.7, $HOCH_2CH_2CH$CH), 3.15 (1H, ddd, *J* = 8.1, 5.8, 3.7, OCH_2CHCH), 3.78 (3H, s, $ArOCH_3$), 3.78–3.86 (2H, m, CH_2OH), 4.08 (1H, dd, *J* = 9.5, 5.8, OCHH'CHCH), 4.48 (1H, d, *J* = 15.2, CHH'Ar), 4.64 (1H, dd, *J* = 9.5, 8.1, OCHH'CHCH), 4.78 (1H, d, *J* = 15.2, CHH'Ar), 6.82 (2H, d, *J* = 8.7, ArH), 7.01 (2H, d, *J* = 8.7, ArH); δ_C (126 MHz, $CDCl_3$) 27.9 (CH_3), 33.7 (CH_2), 45.0 (CH), 45.9 (CH_2), 46.4 (CH), 55.3 (CH_3), 61.0 (CH_2), 71.0 (CH_2), 71.3 (C), 85.2 (C), 113.8 (CH), 128.6 (CH), 130.1 (C), 159.1 (C), 166.9 (C(O)), 170.3 (C(O)), 176.3 (C(O)); *m/z* LRMS (ESI+) 428 ($[M+Na]^+$, 100%); HRMS found $[M+Na]^+$ 428.1673, $[C_{22}H_{27}NNaO_6]^+$ requires 428.1680; $[\alpha]_D$ (25 °C) +22.7 (c = 0.52 in CH_2Cl_2), lit. $[\alpha]_D$ +67.3 (c = 0.52 in CH_2Cl_2); data in accordance with literature.[13] We have shown that the e.e. of our synthetic material is >95% by chiral stationary phase HPLC analysis, see page S66 for the relevant chromatogram.

Comparison with literature data



Comparison of ^{1}H NMR values[13], [a]

Entry	Assignment	Synthetic δ_H / ppm (500 MHz, $CDCl_3$)	Lit. δ_H[b] / ppm (400 MHz, $CDCl_3$)	$\lvert\Delta\delta_H\rvert$ / ppm
1	$CH_2C(CHCH)_2$	7.28, 2H, d	7.29, 2H, d	0.01
2	$MeOC(CHCH)_2$	6.82, 2H, d	6.80, 2H, d	0.02
3	CHHAr	4.77, 1H, d	4.79, 1H, d	0.02
4	14	4.64, 1H, dd	4.65, 1H, dd	0.01
5	CHHAr	4.48, 1H, d	4.49, 1H, d	0.01
6	14’	4.08, 1H, dd	4.08, 1H, d	0.00
7	13	3.87—3.77, 2H, m	3.87—3.79, 2H, m	n/a
8	OCH_3	3.77, 3H, s	3.78, 3H, s	0.01
9	3	3.14, 1H, ddd	3.15,[c] 1H, m	0.01
10	2	2.61, 1H, ddd	2.60, 1H, m	0.01
11	OH	2.54, 1H, t	2.38, 1H, br	0.16
12	12	1.99, 1H, dddd	1.99, 1H, m	0.00
13	12’	1.78, 1H, dddd	1.77, 1H, m	0.01
14	$C(CH_3)_3$	1.46, 9H, s	1.47, 9H, s	0.01

[a] We are very grateful to Professor Danishefsky for providing copies of the original NMR spectra

[b] All literature data have been corrected by +0.07 ppm as the original spectrum was referenced with $CHCl_3$ solvent residual at 7.20 ppm rather than 7.27 ppm.

[c] Reported in the Supporting Information of Ref. [13] as 3.26 (after correction). The value given here is measured from the original spectrum kindly supplied by Professor Danishefsky.

Comparison of ^{13}C NMR values[13]

Entry	Assignment	Synthetic δ_C / ppm (126 MHz, $CDCl_3$)	Lit. δ_C[a] / ppm (100 MHz, CDCl3)	$\lvert\Delta\delta_C\rvert$ / ppm
1	1	176.3	176.4	0.1
2	15	170.3	170.3	0.0
3	5	166.9	166.8	0.1
4	$MeOC(CHCH)_2$	159.1	158.9	0.2
5	$CH_2C(CHCH)_2$	130.1	130.1	0.0
6	$CH_2C(CHCH)_2$	128.6	128.5	0.1
7	$CH_2C(CHCH)_2$	113.8	113.7	0.1
8	$C(CH_3)_3$	85.2	85.1	0.1
9	4	71.3	71.3	0.0
10	14	71.0	70.9	0.1
11	13	61.0	60.5	0.5
12	OCH_3	55.3	55.2	0.1
13	2	46.4	46.1	0.3
14	CH_2Ar	45.9	45.7	0.2
15	3	45.0	44.6	0.4
16	12	33.7	33.5	0.2
17	$C(CH_3)_3$	27.9	27.8	0.2

[a] All literature data have been corrected by –0.38 ppm as the original spectrum was referenced with the central $CHCl_3$ solvent residual at 77.54 ppm rather than 77.16 ppm, see Reference [13].

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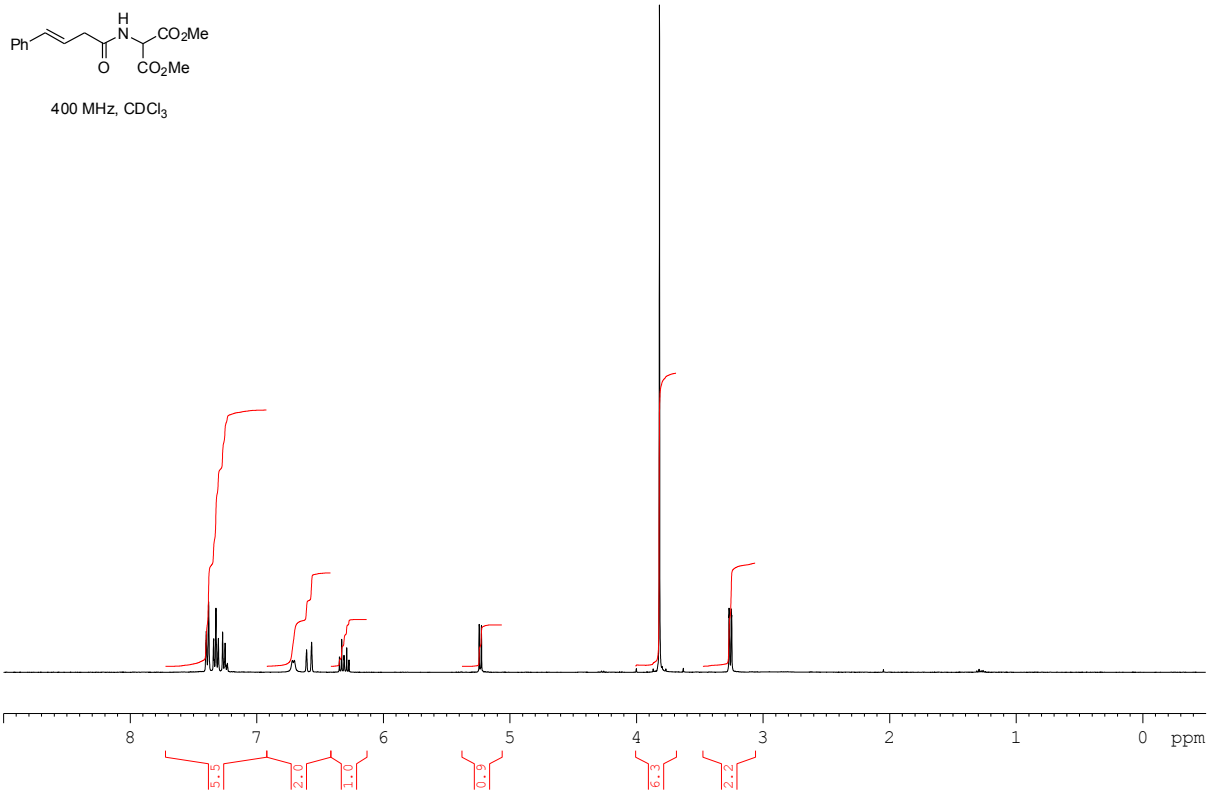
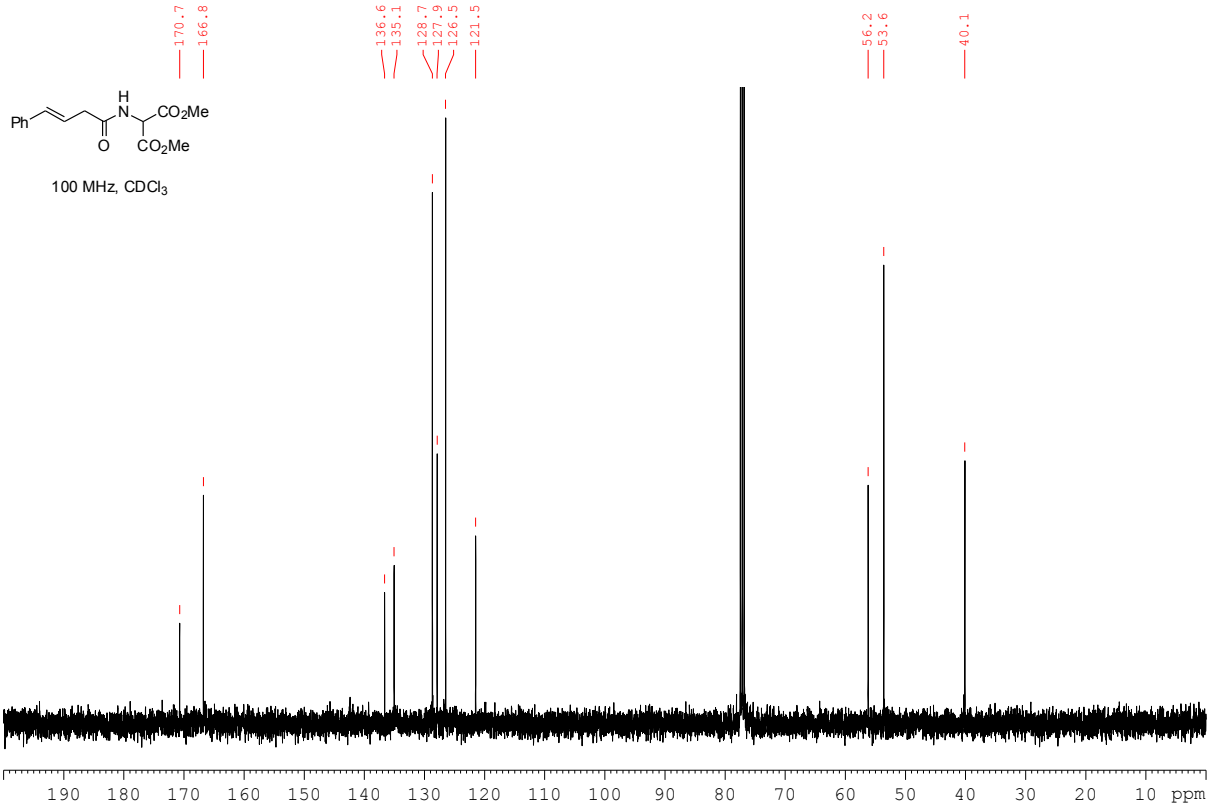
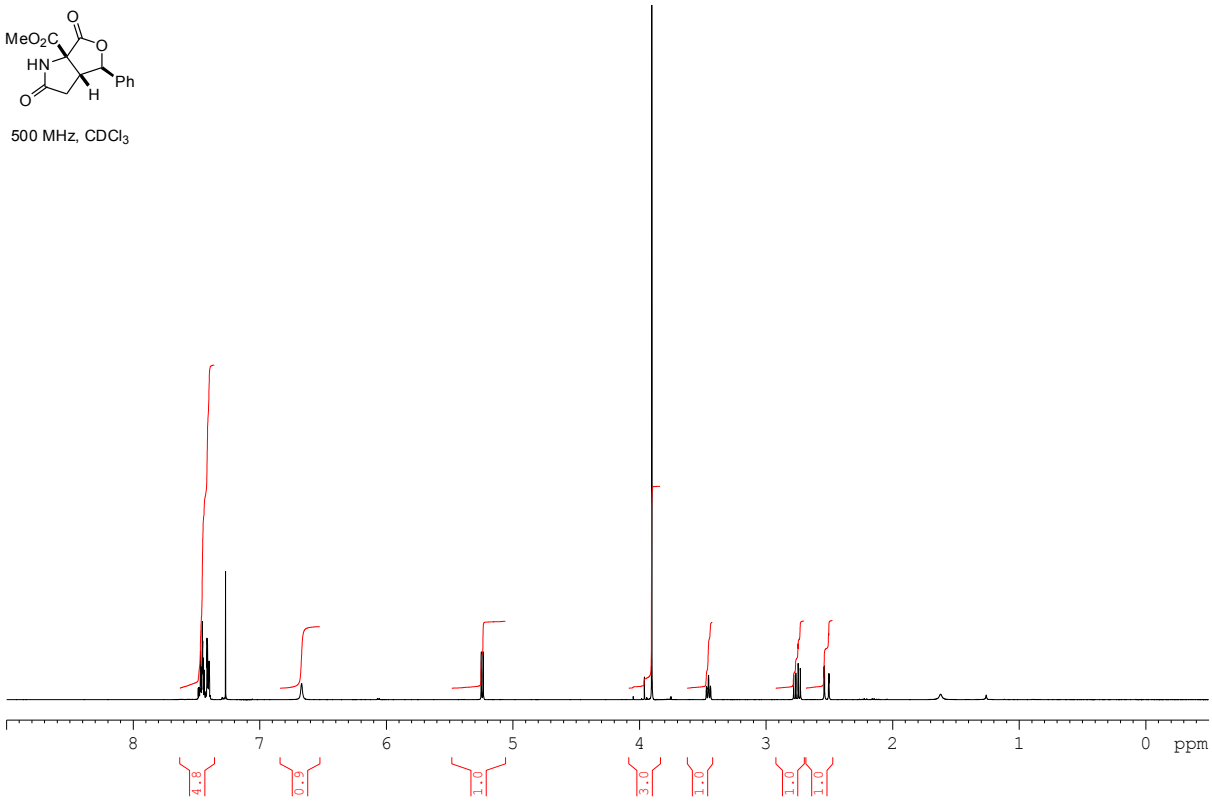
Selected NMR Spectra and HPLC Traces

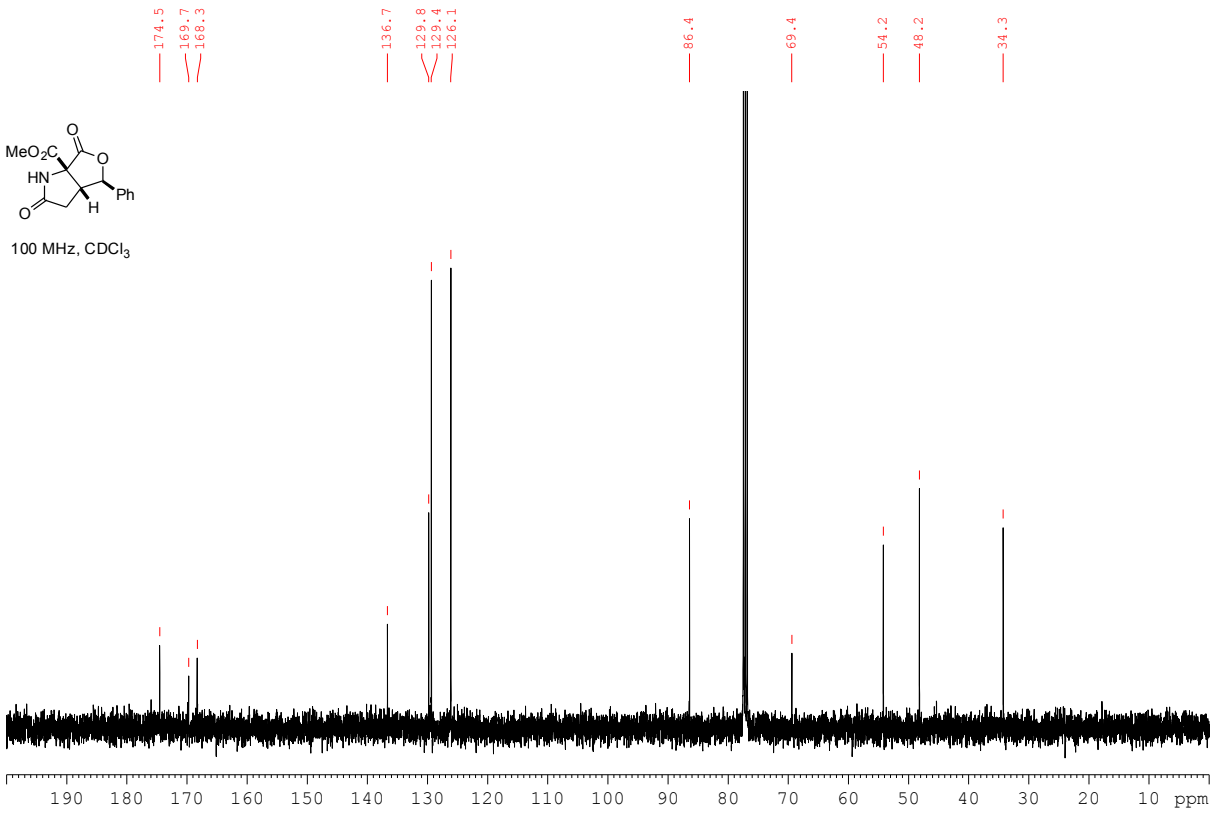
Spectra for compound **7**



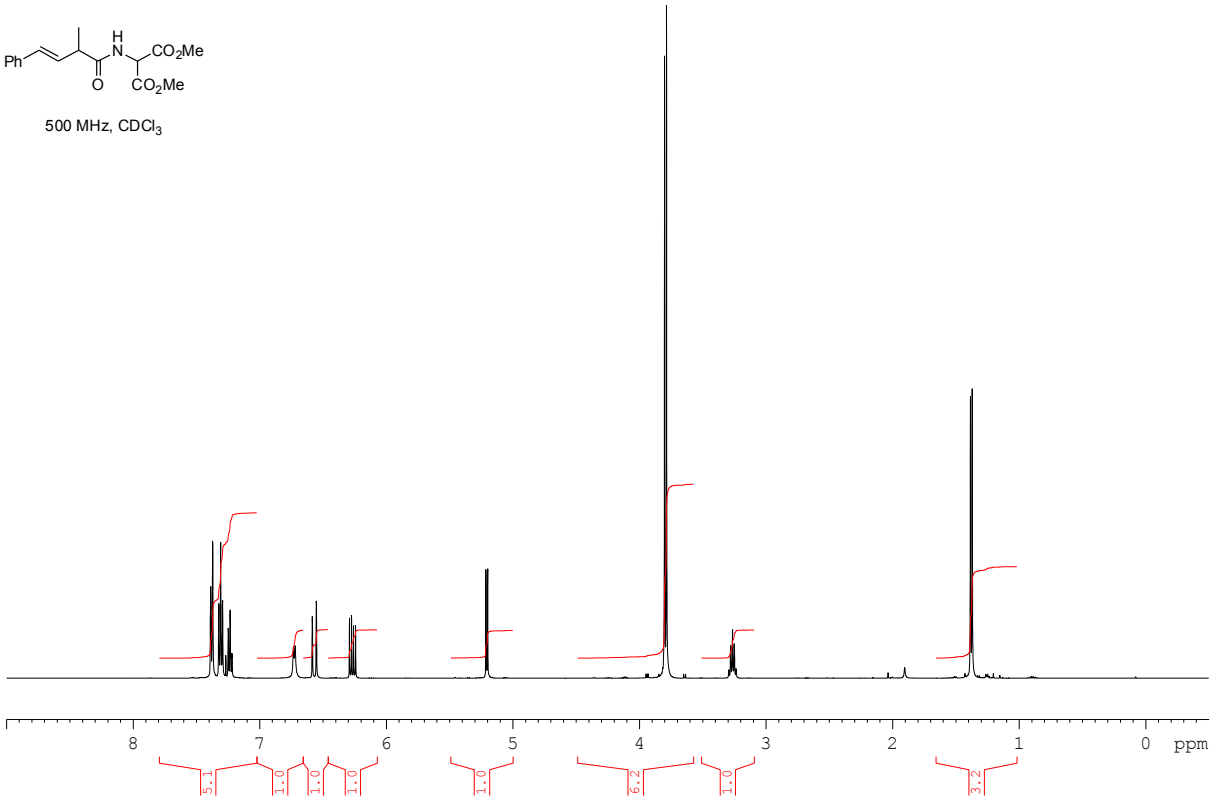


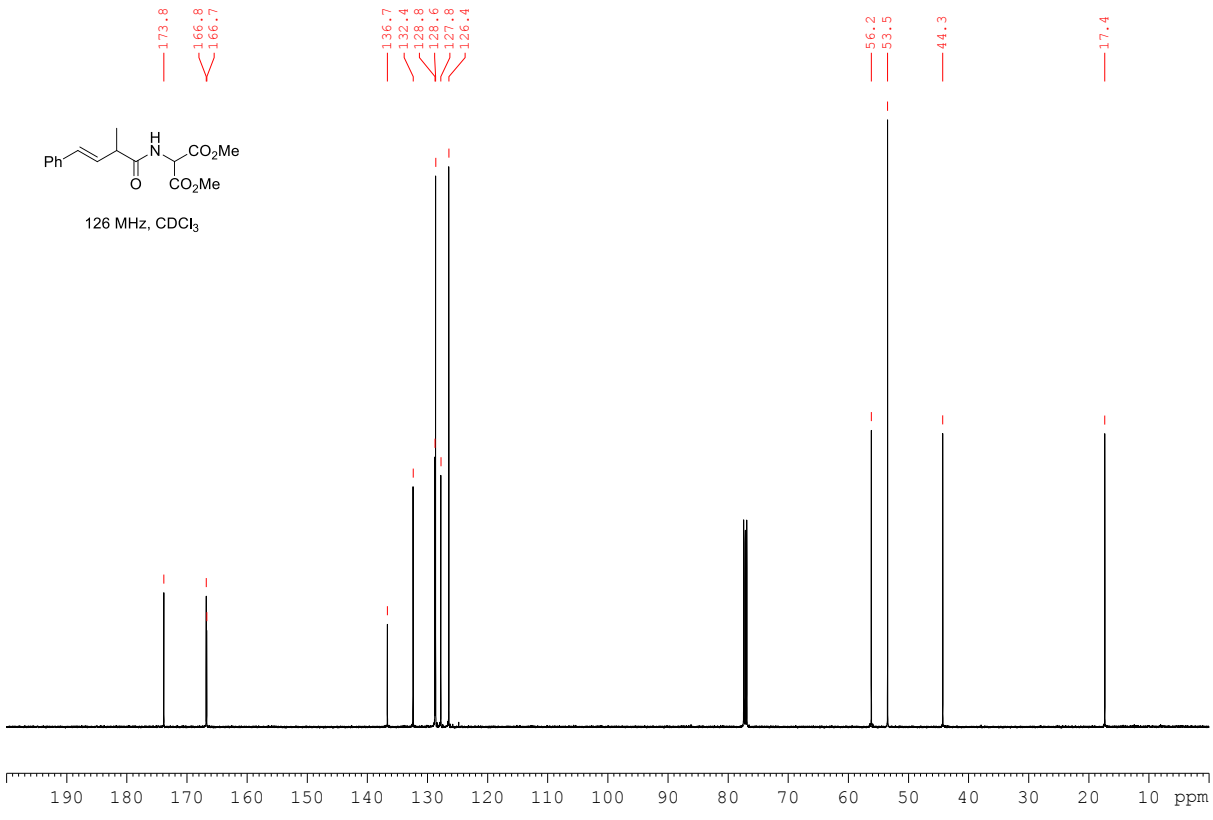
Spectra for compound **8**



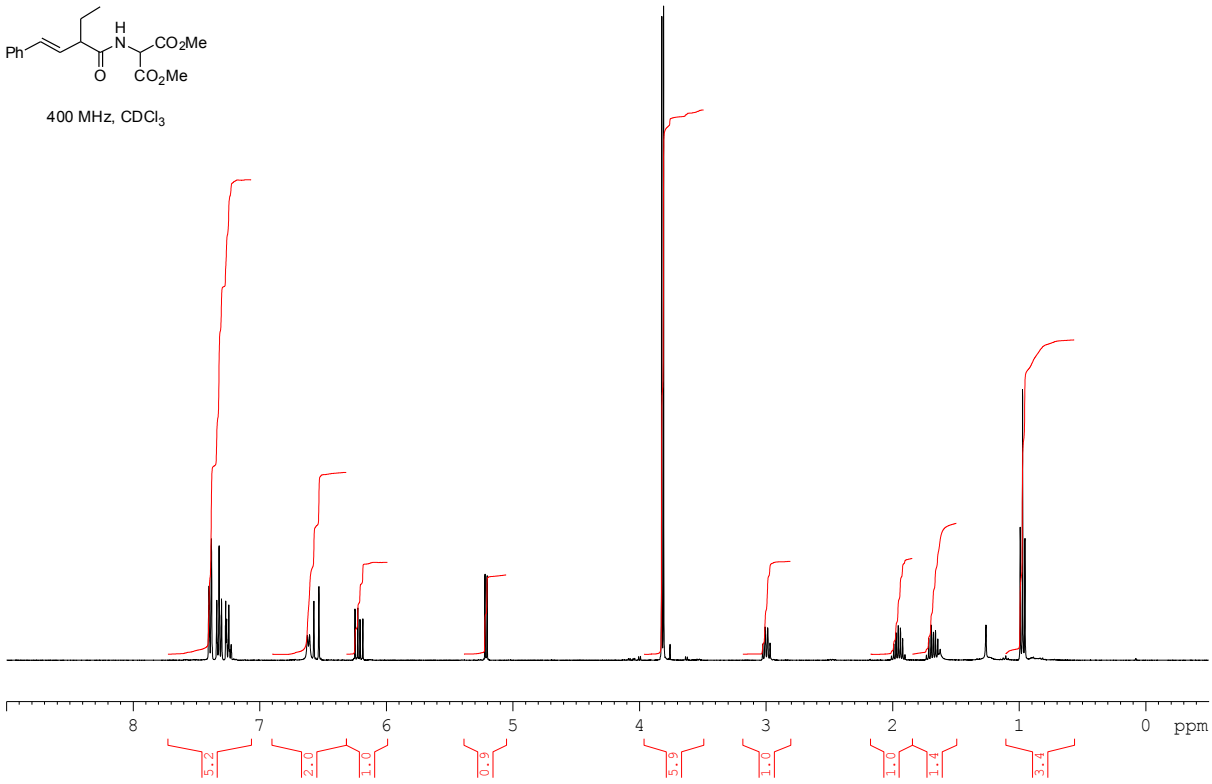


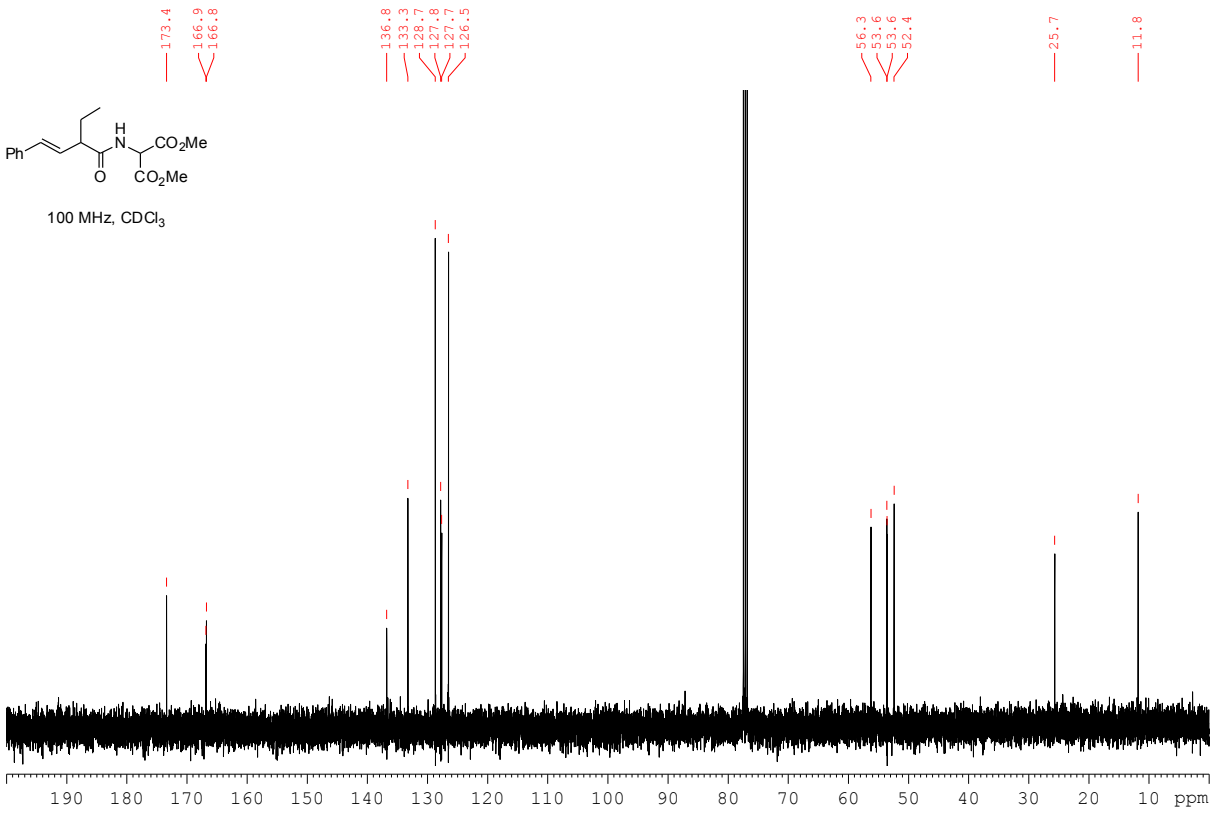
Spectra for compound **9a**



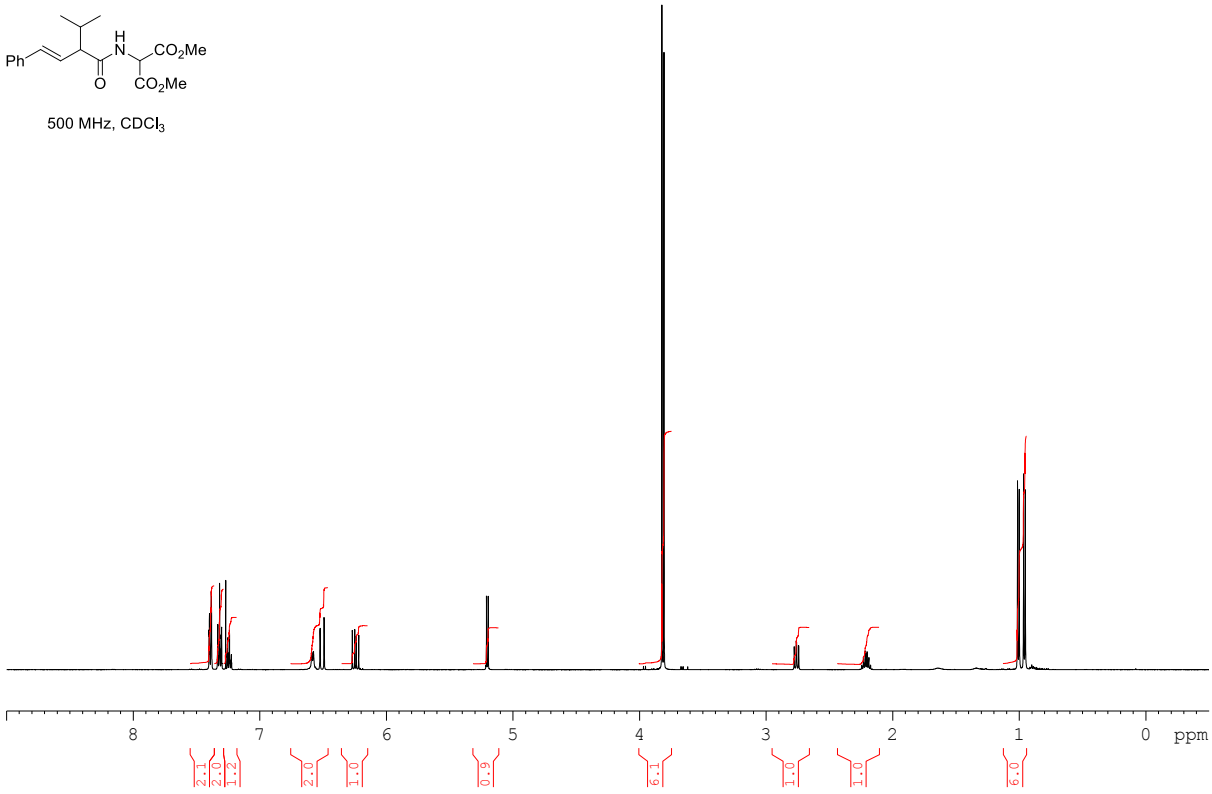


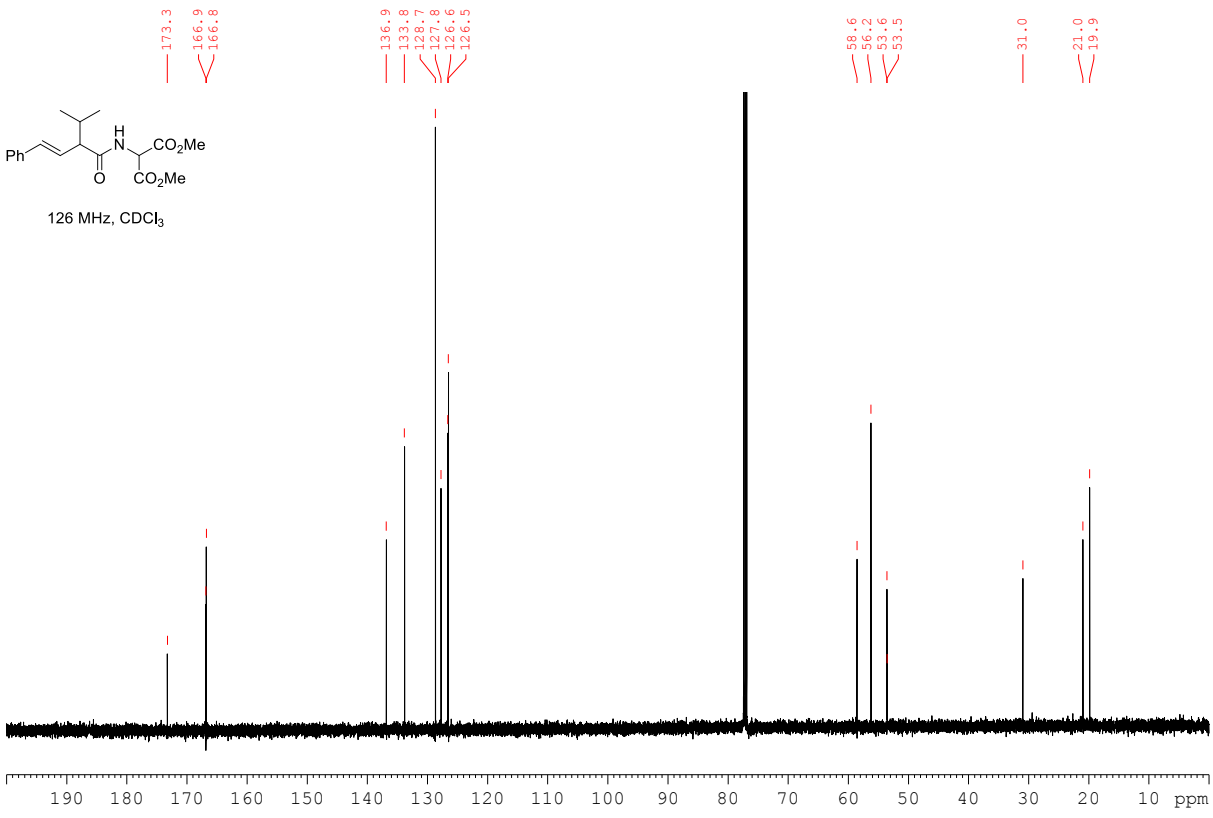
Spectra for compound **9b**



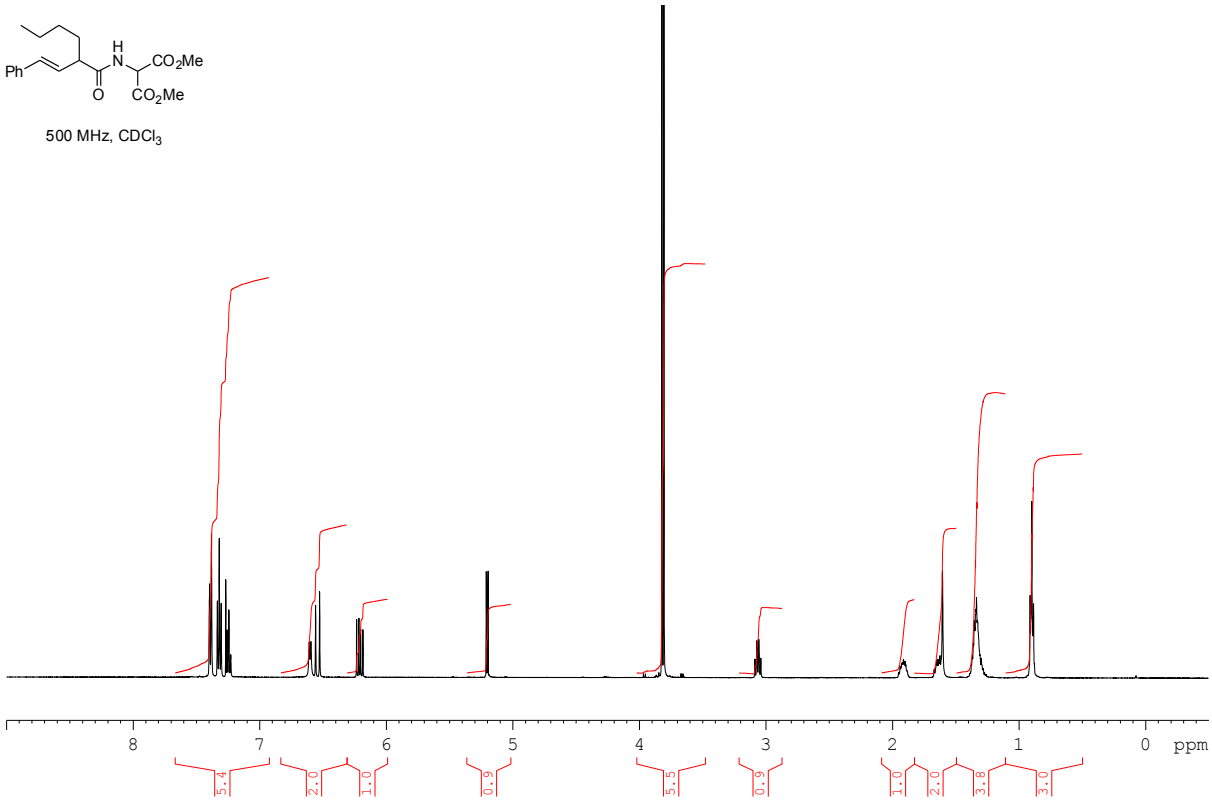


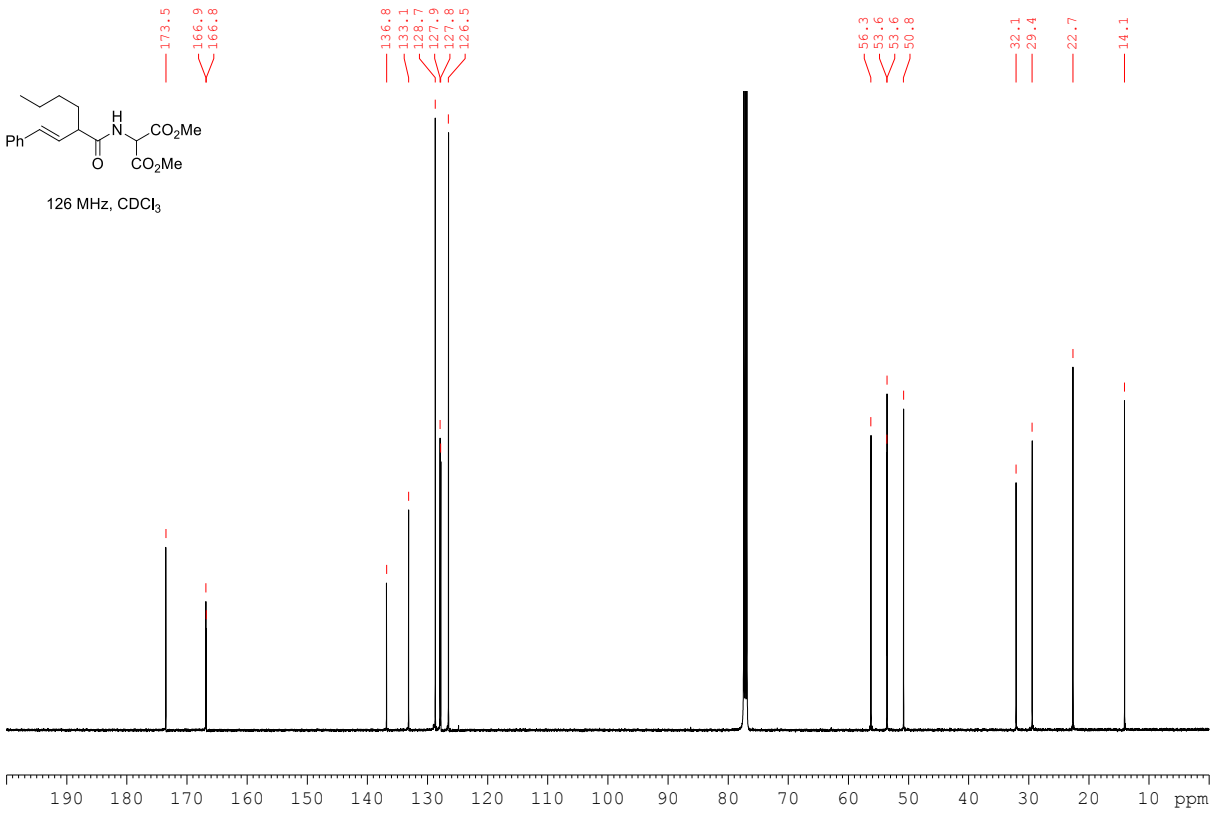
Spectra for compound **9c**



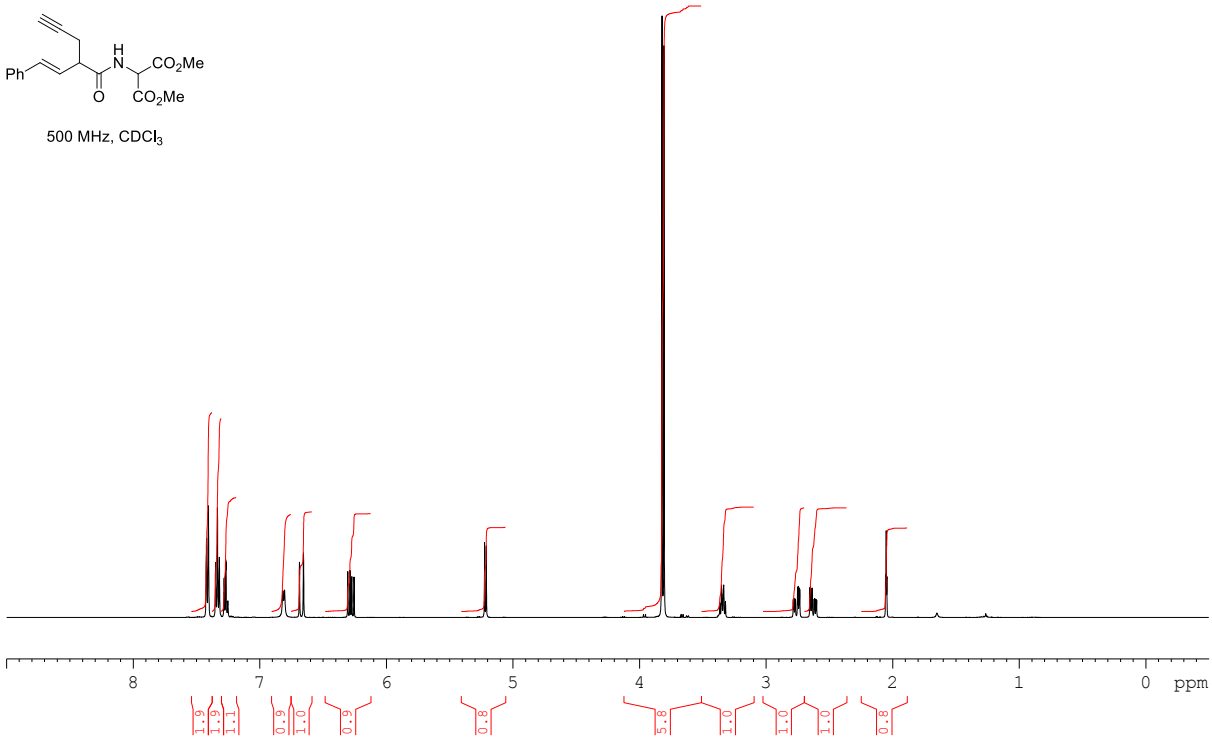


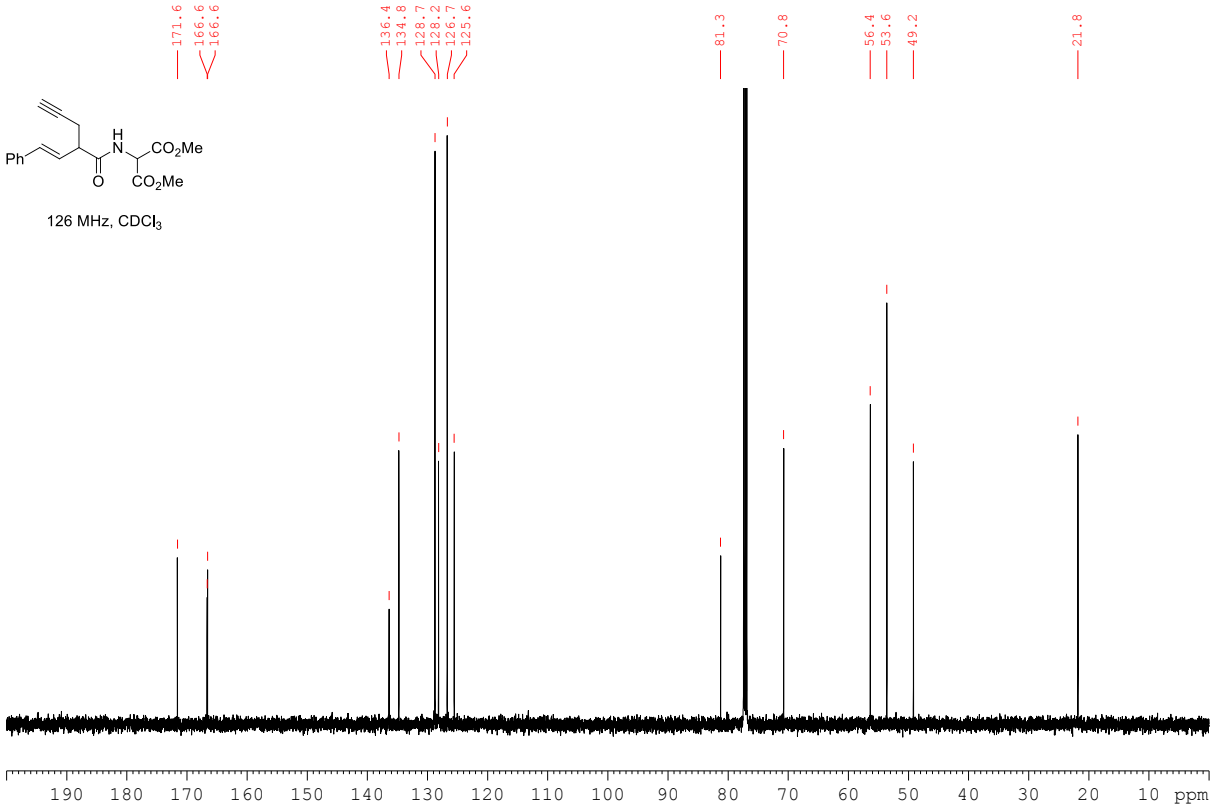
Spectra for compound **9d**



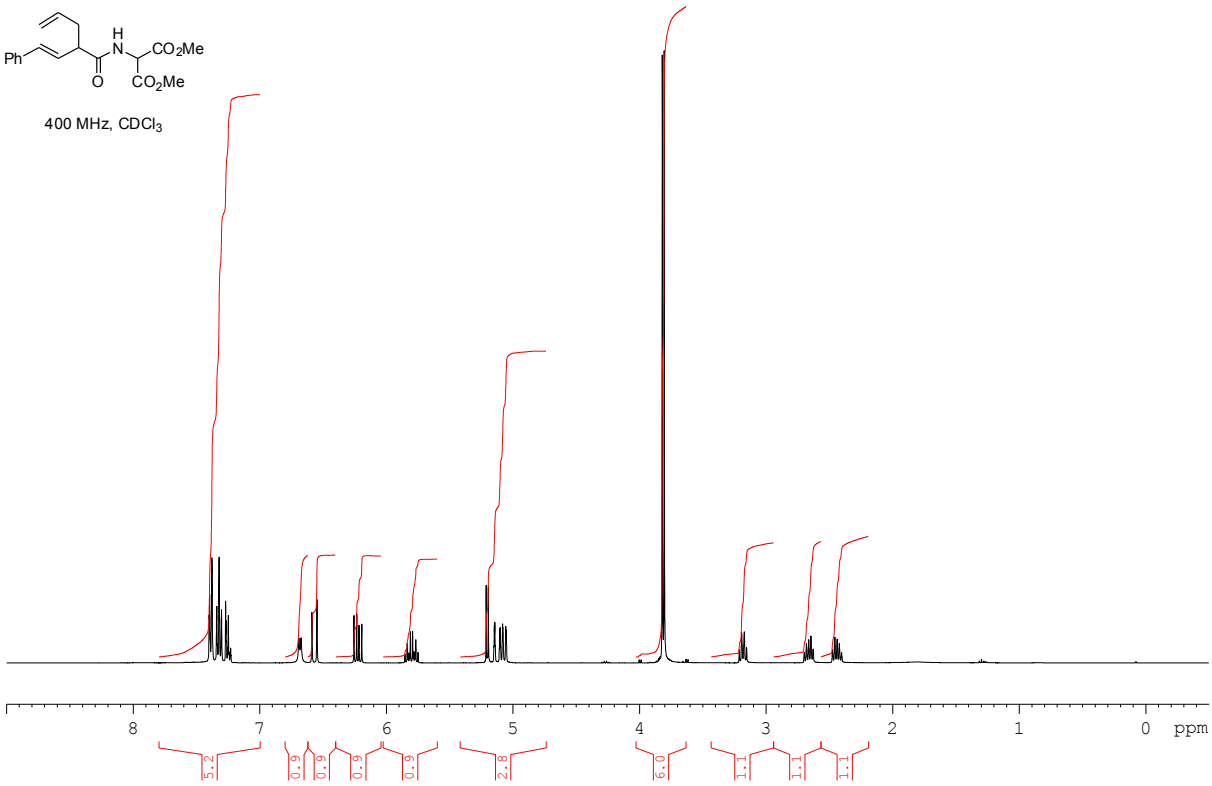


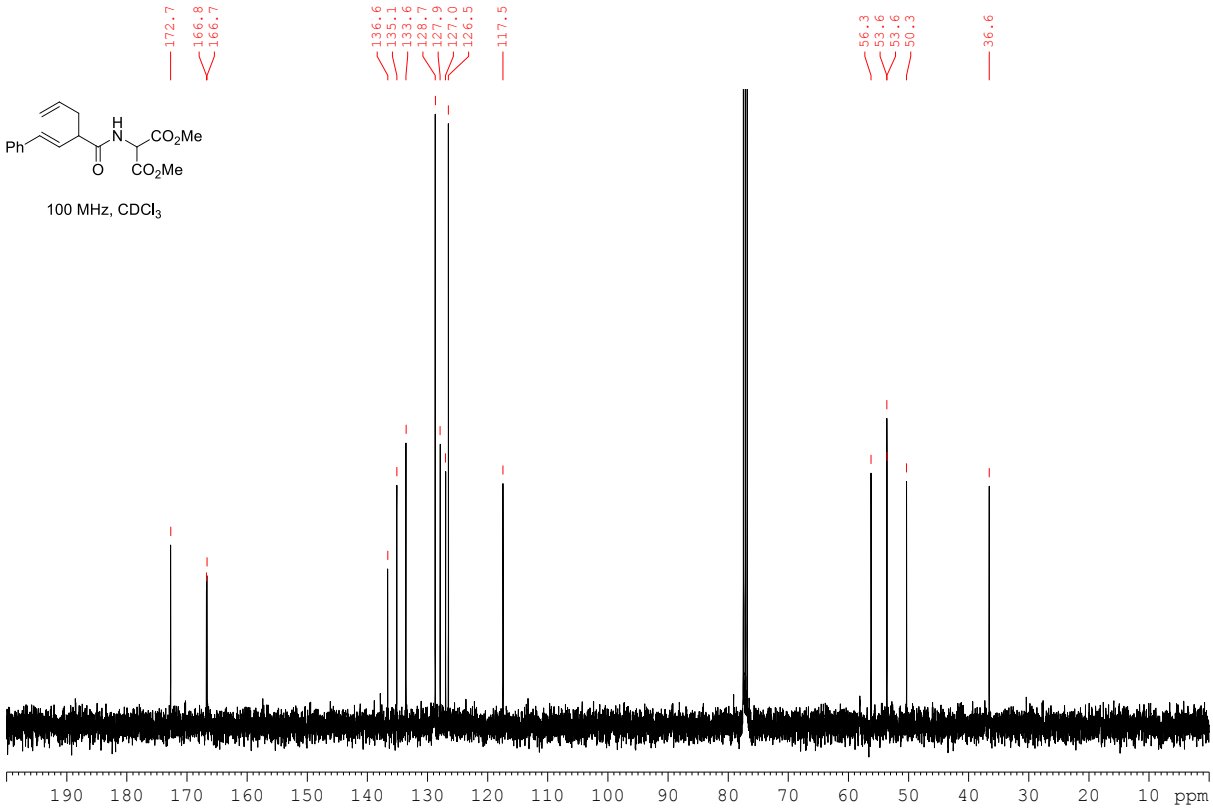
Spectra for compound **9e**



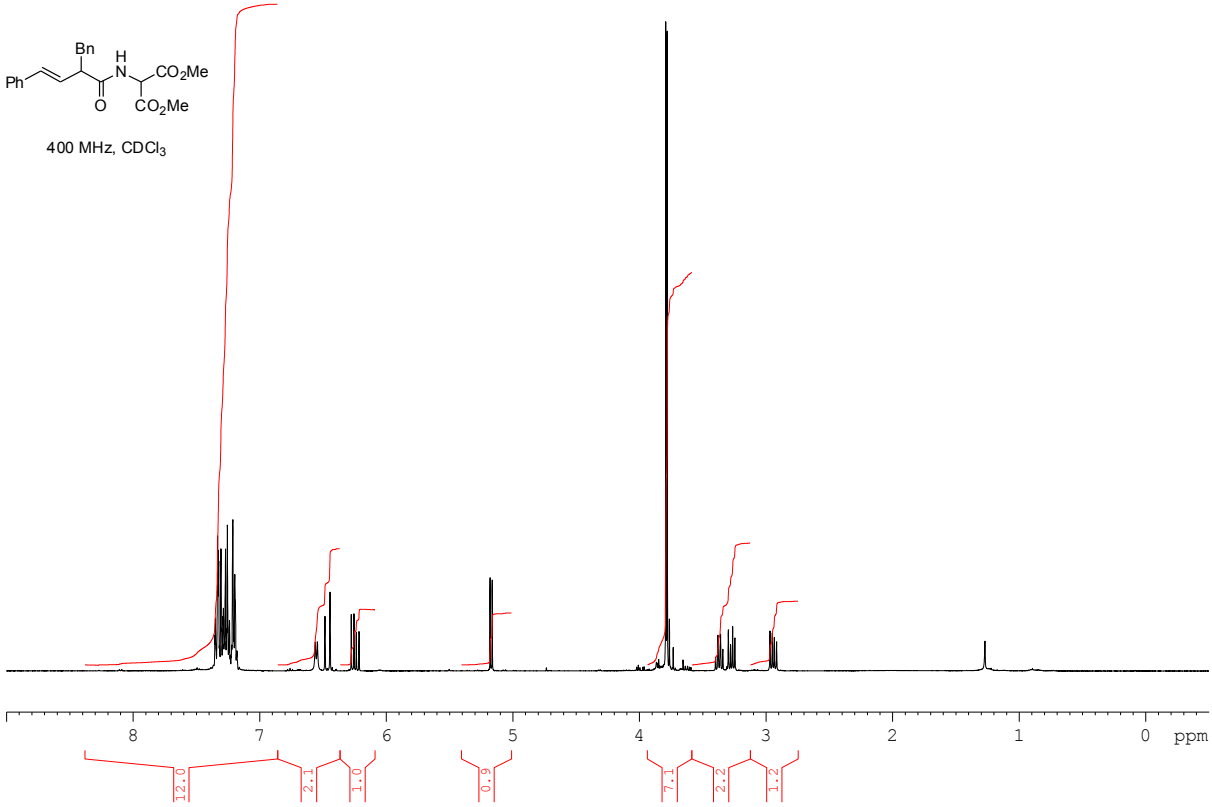


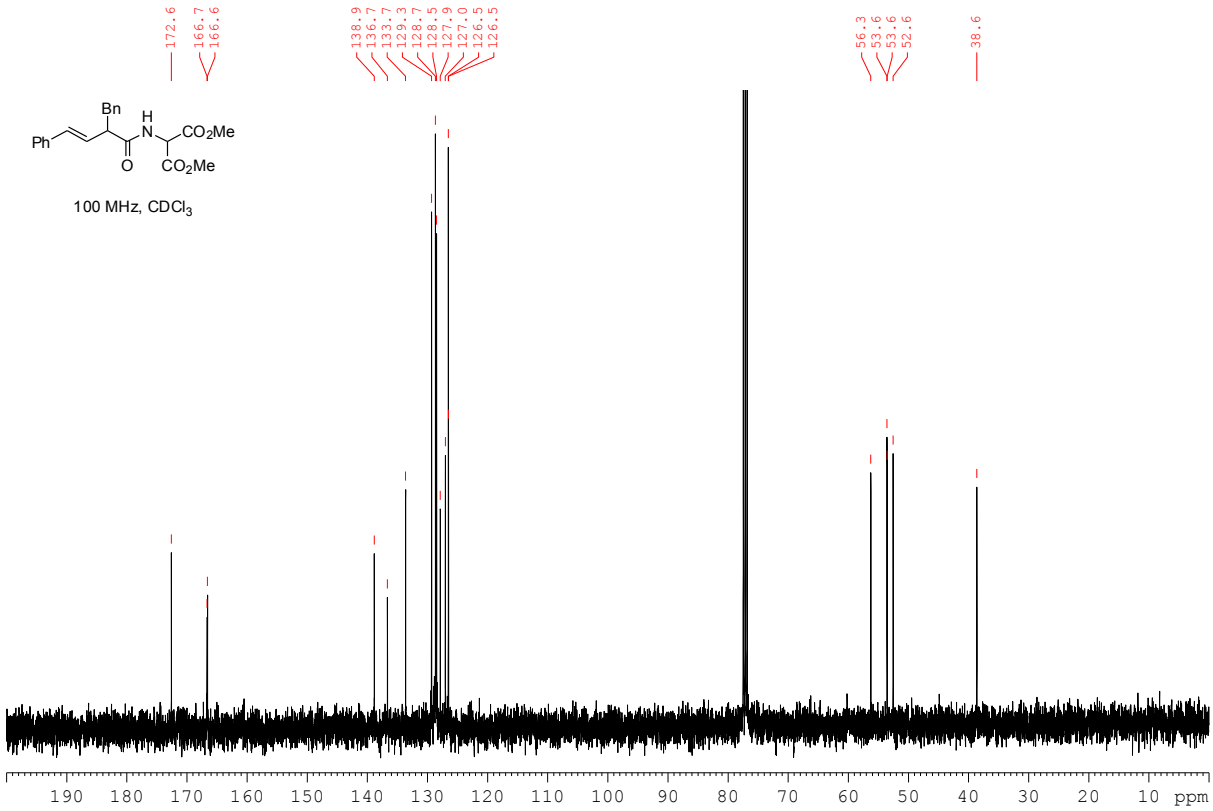
Spectra for compound **9f**



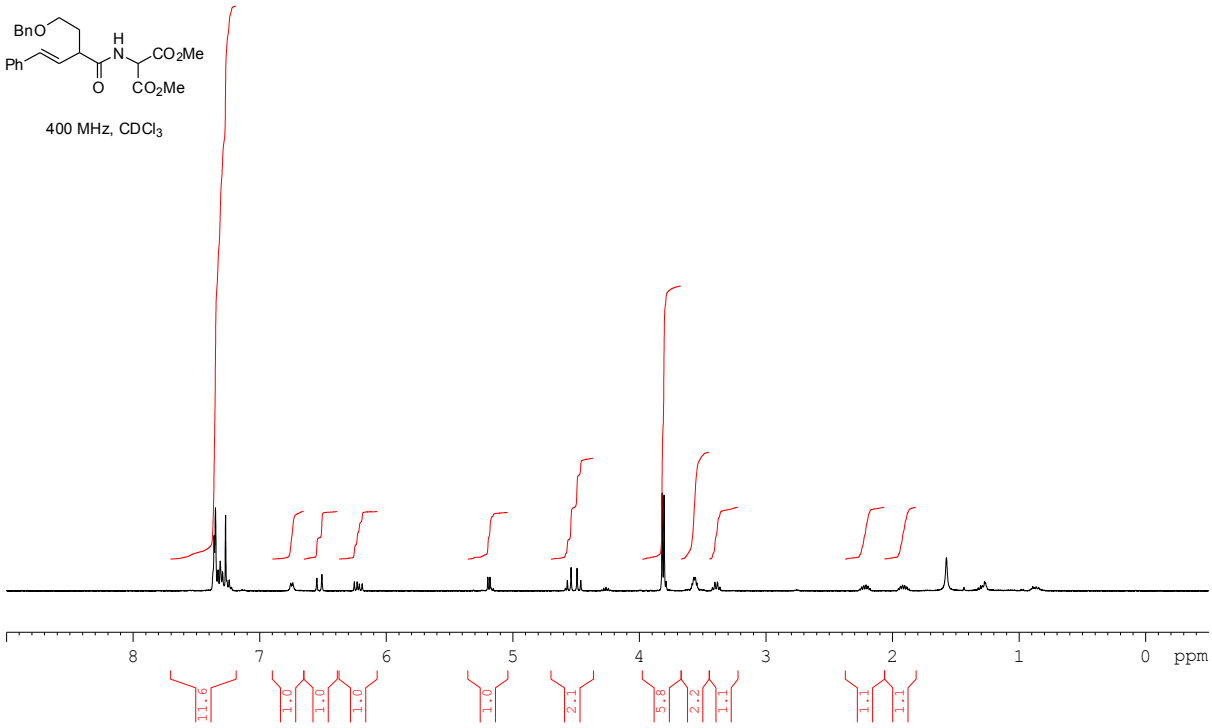


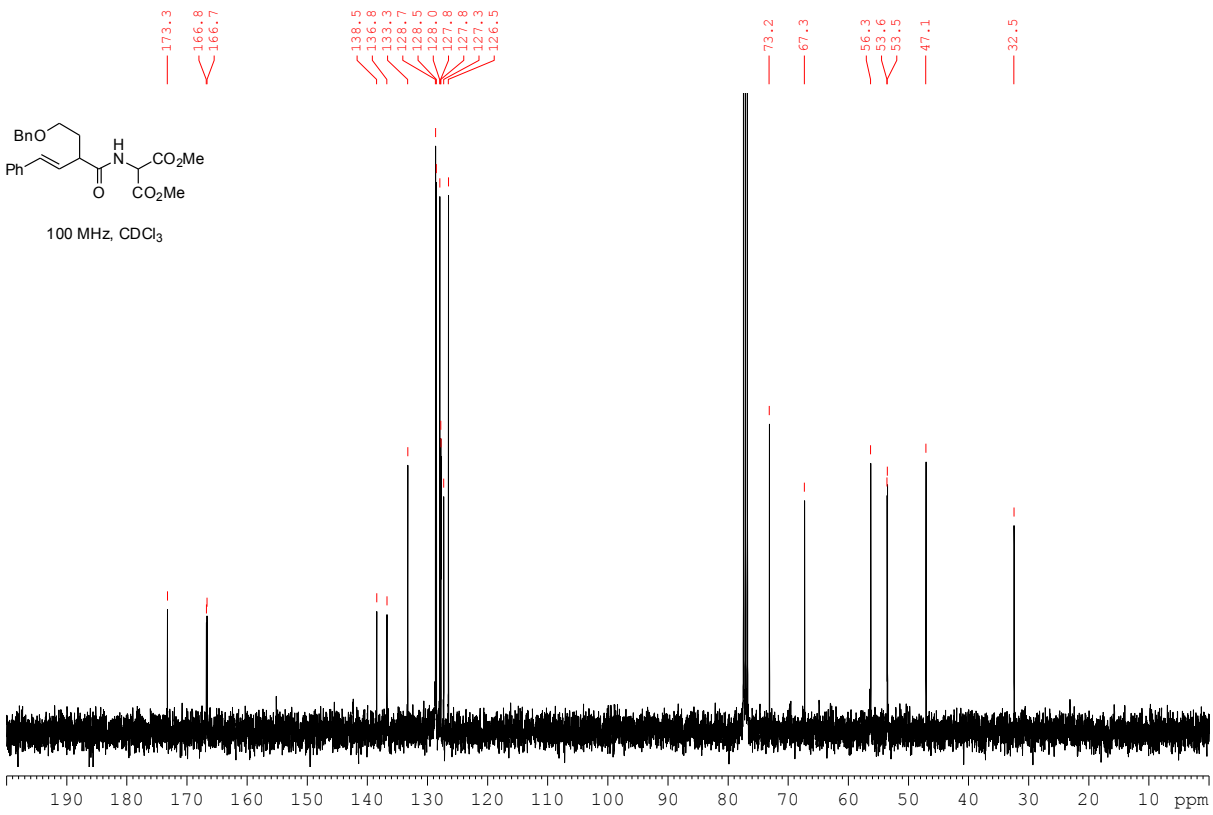
Spectra for compound **9g**



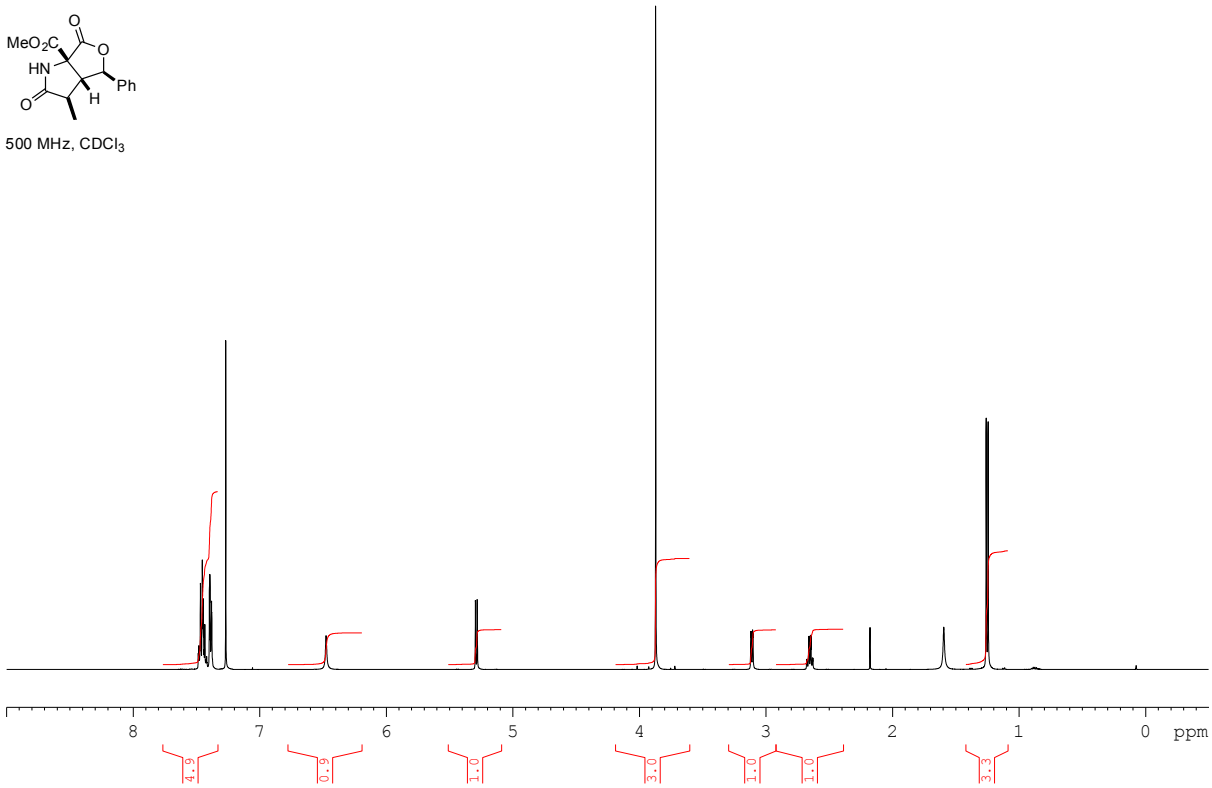


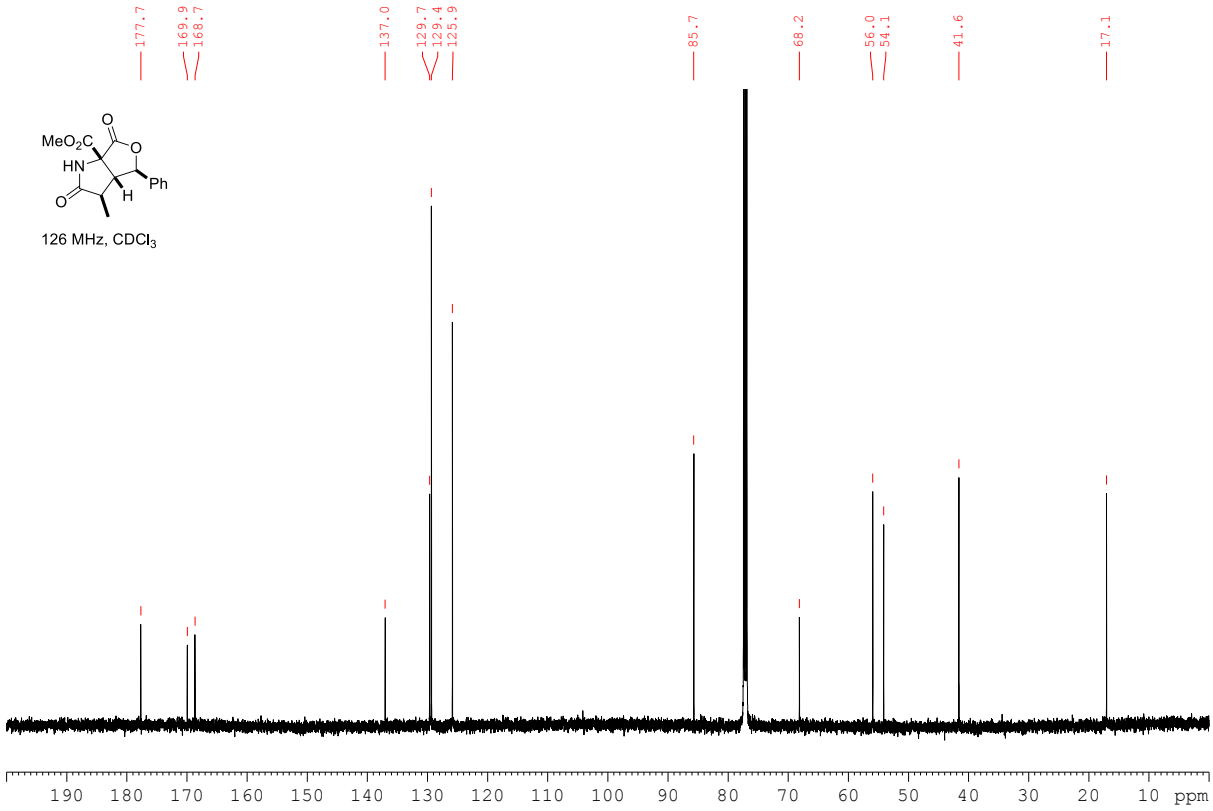
Spectra for compound **9h**



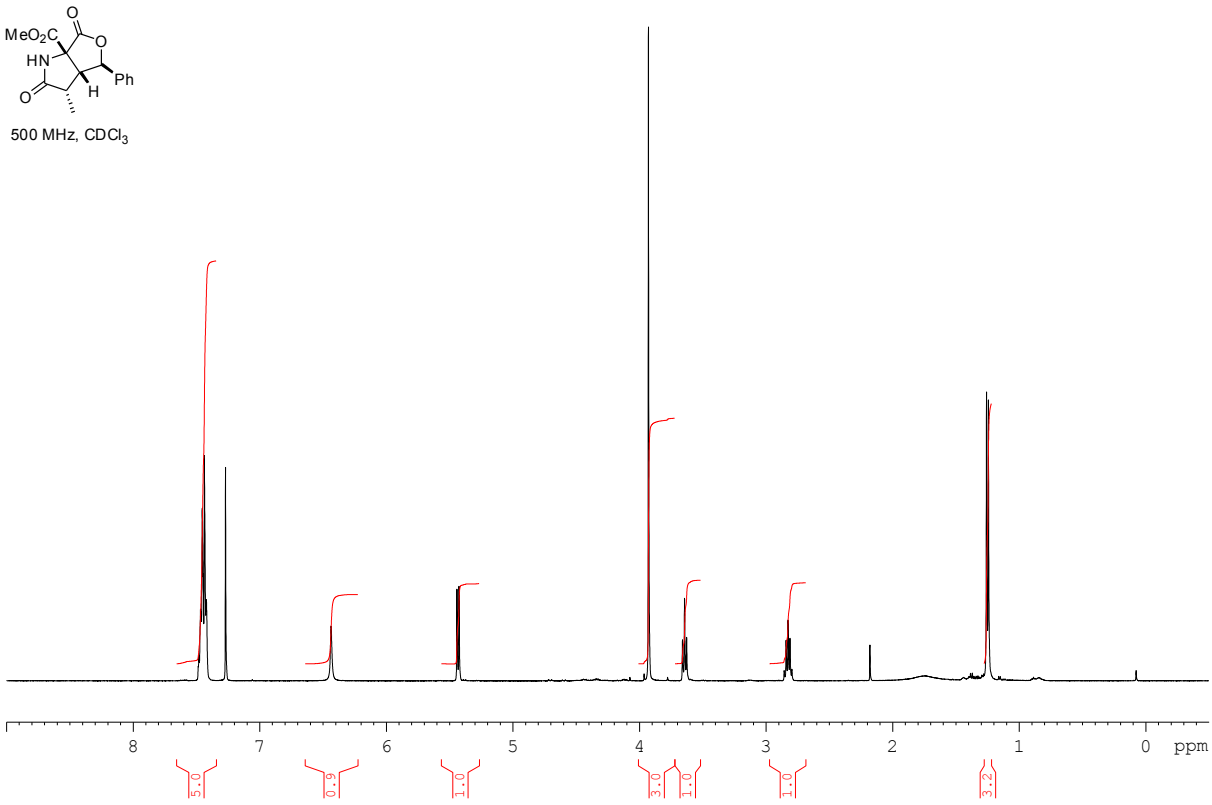


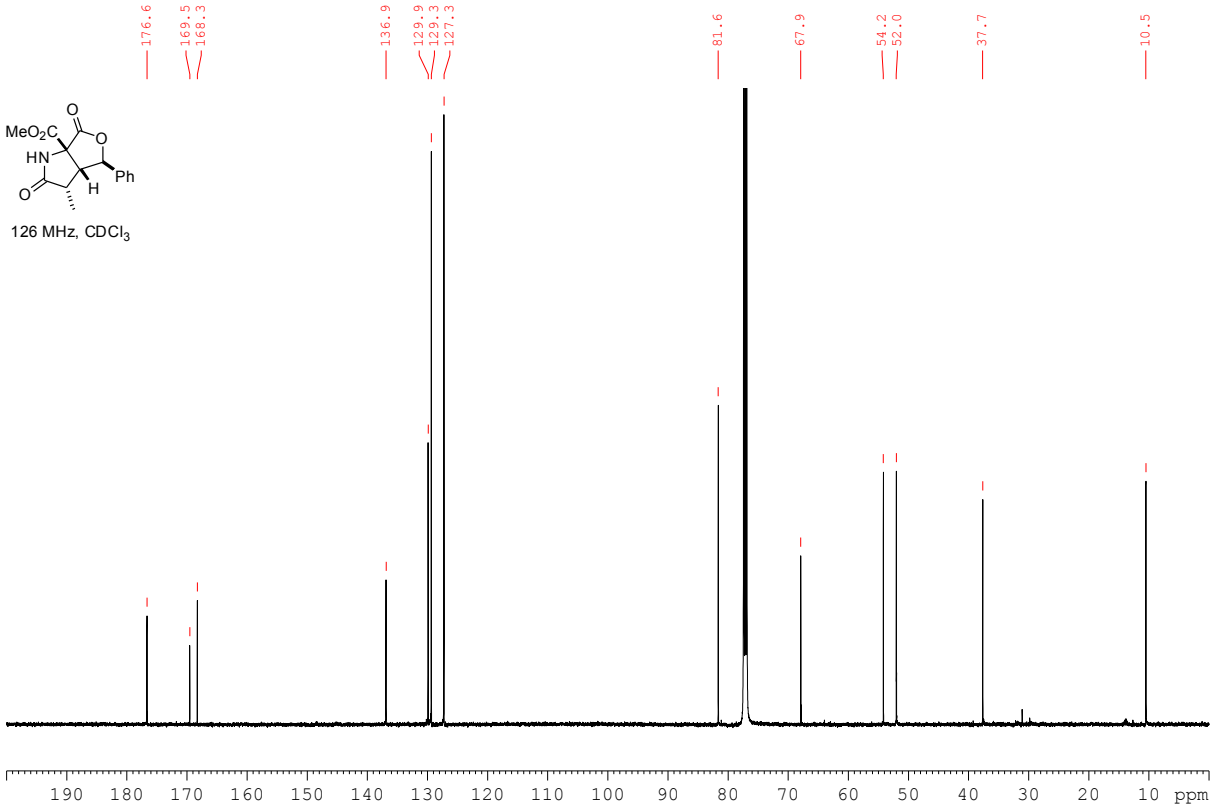
Spectra for compound **10a** (major diastereomer, purified by semi-preparative HPLC)



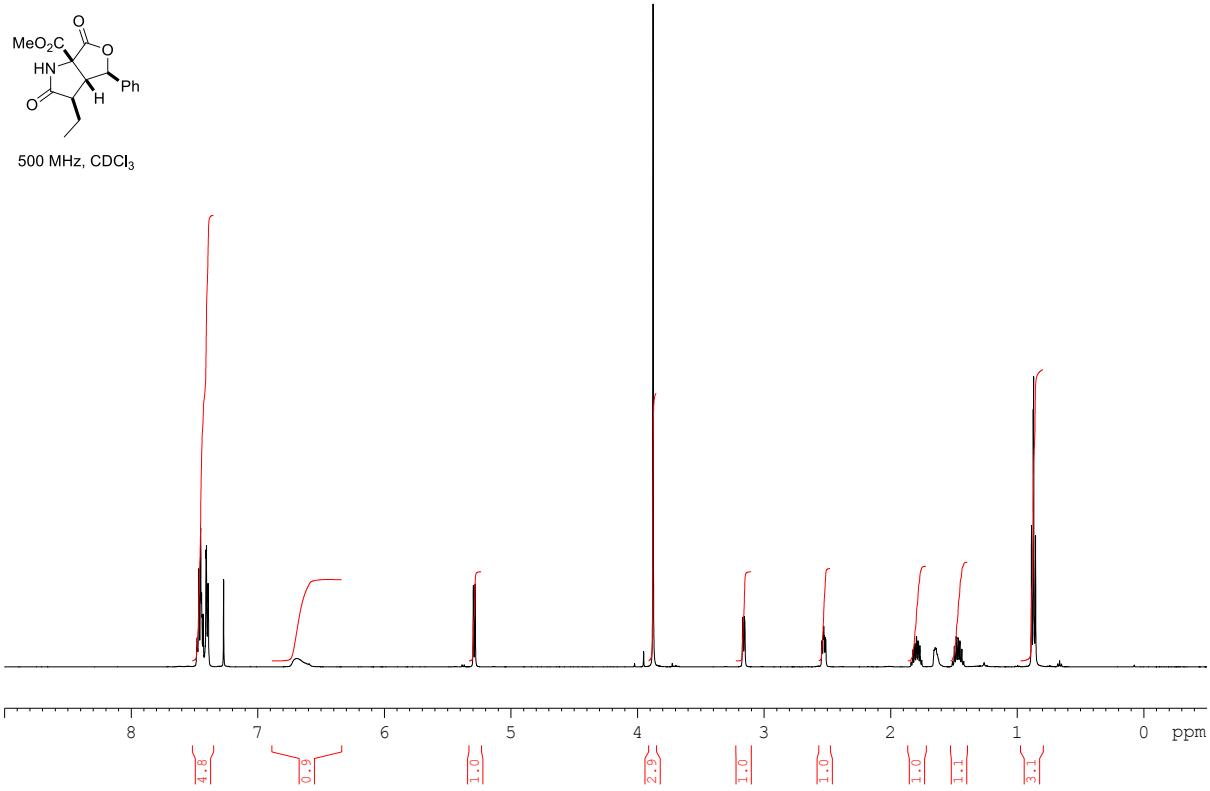


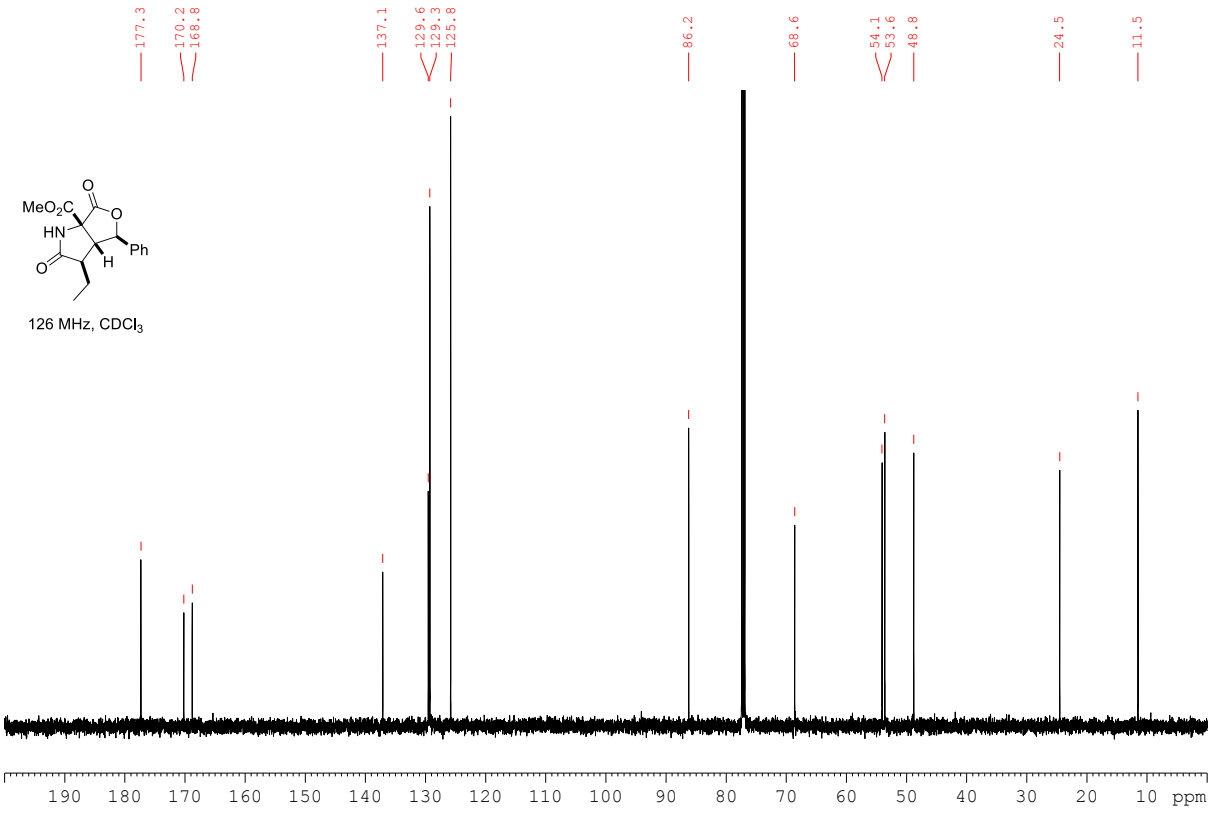
Spectra for compound **10a** (minor diastereomer, purified by semi-preparative HPLC)



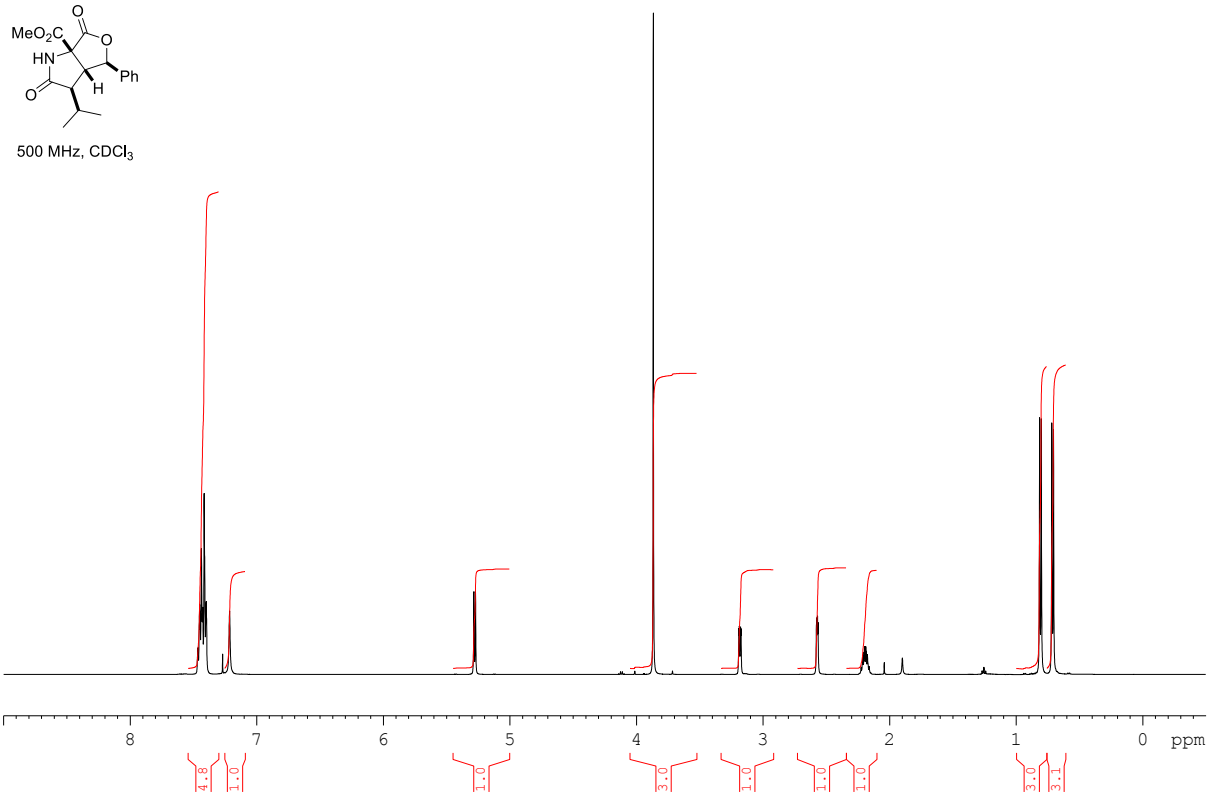


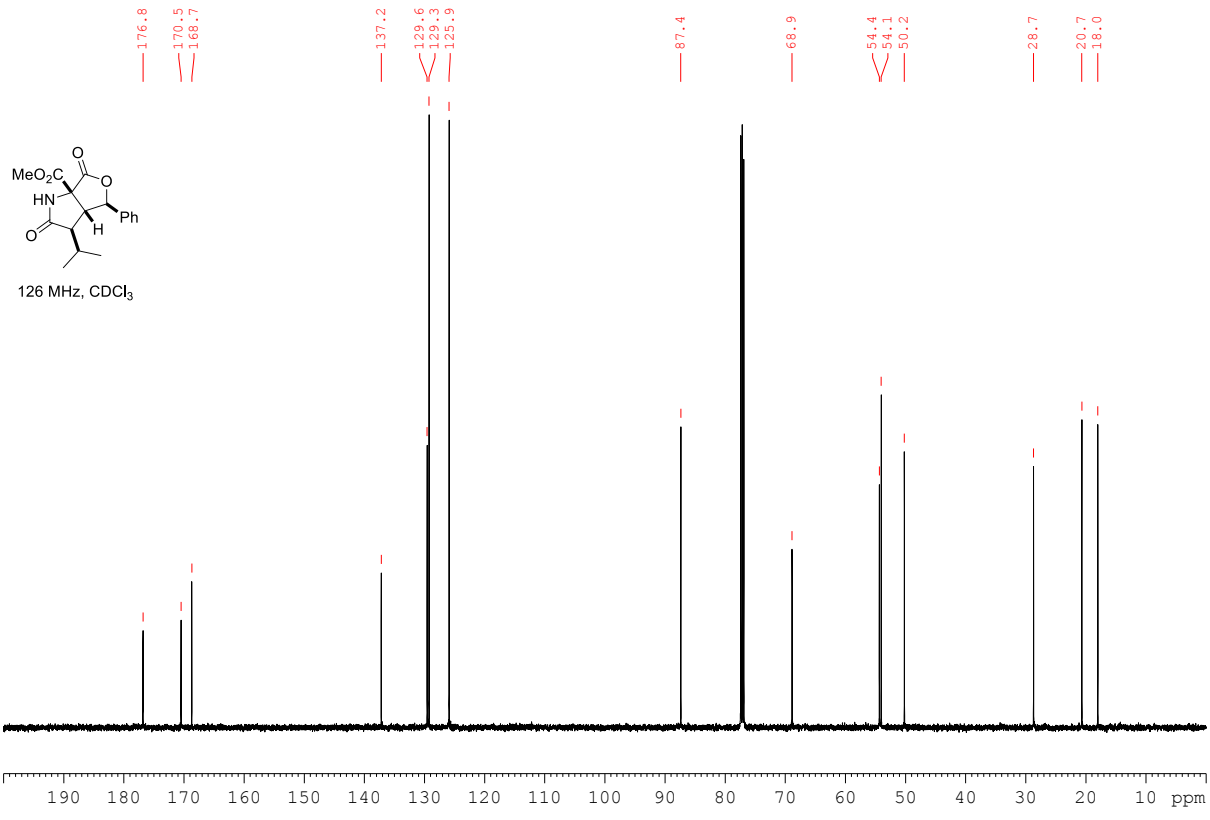
Spectra for compound **10b**



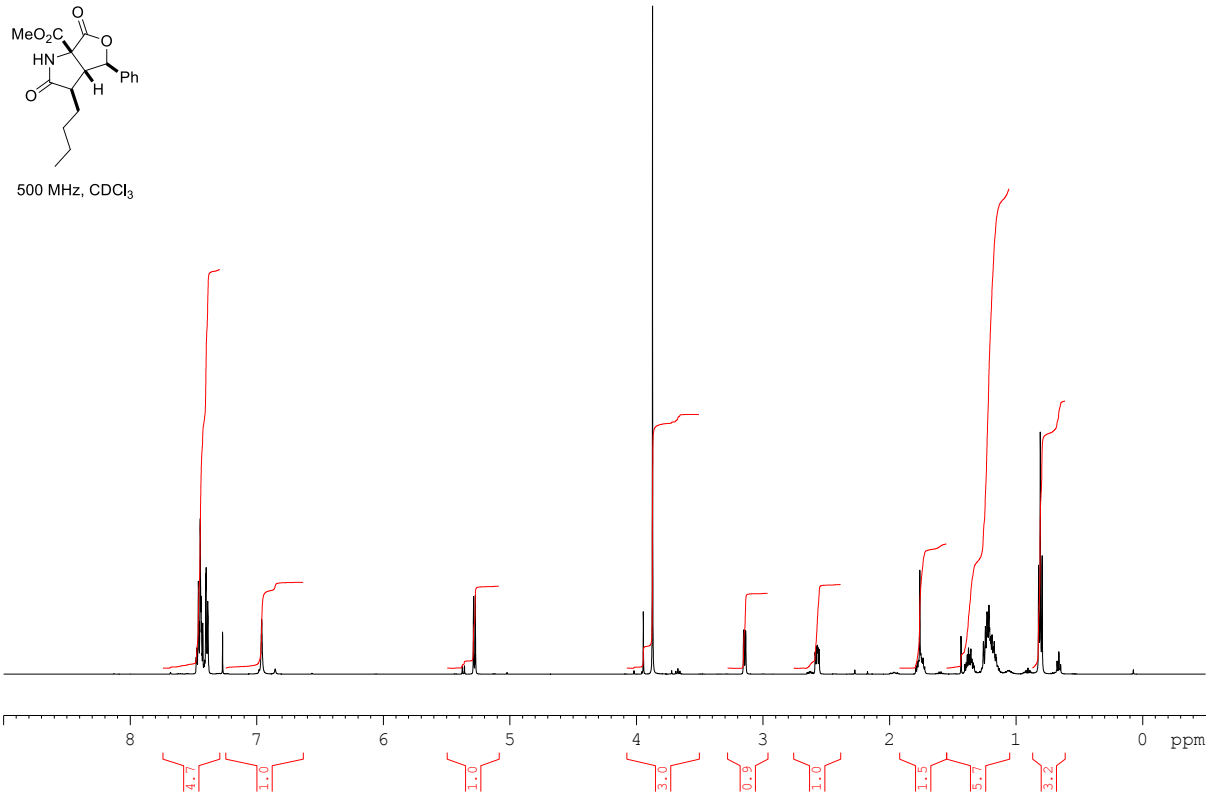


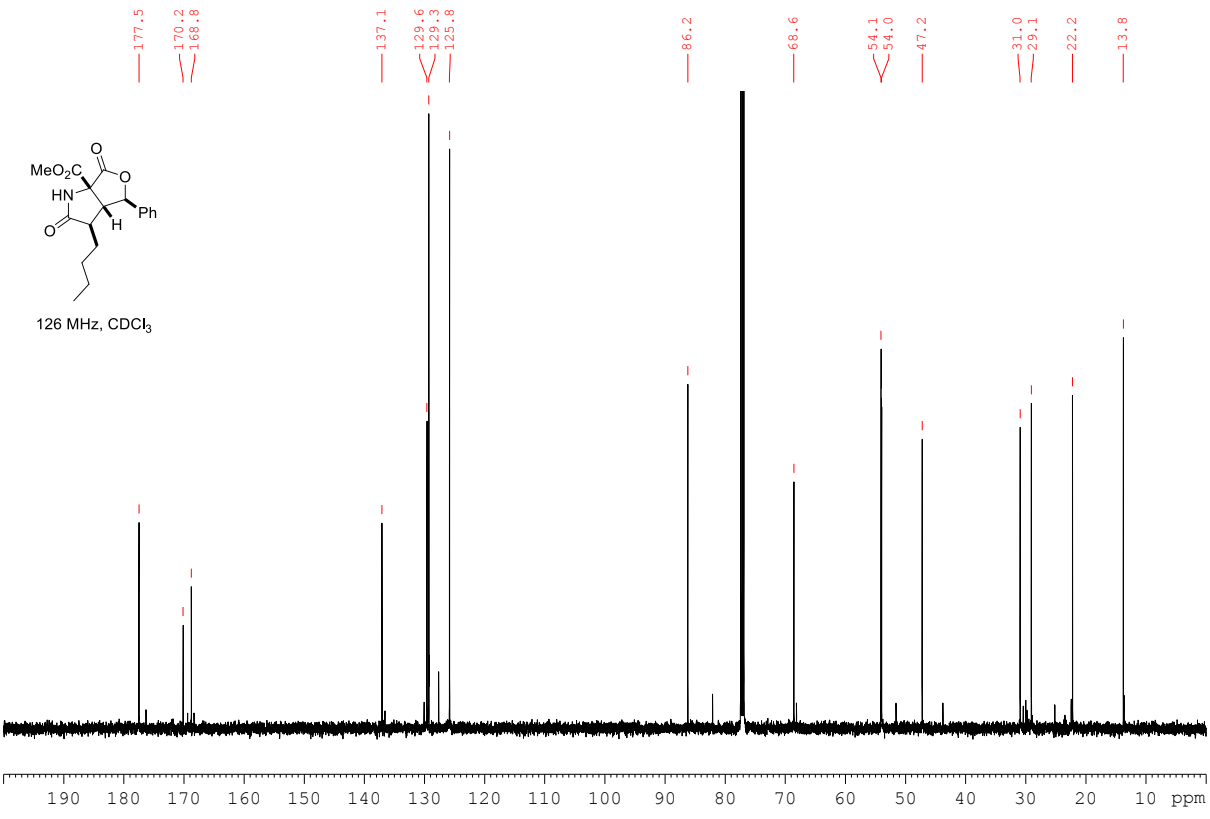
Spectra for compound **10c**



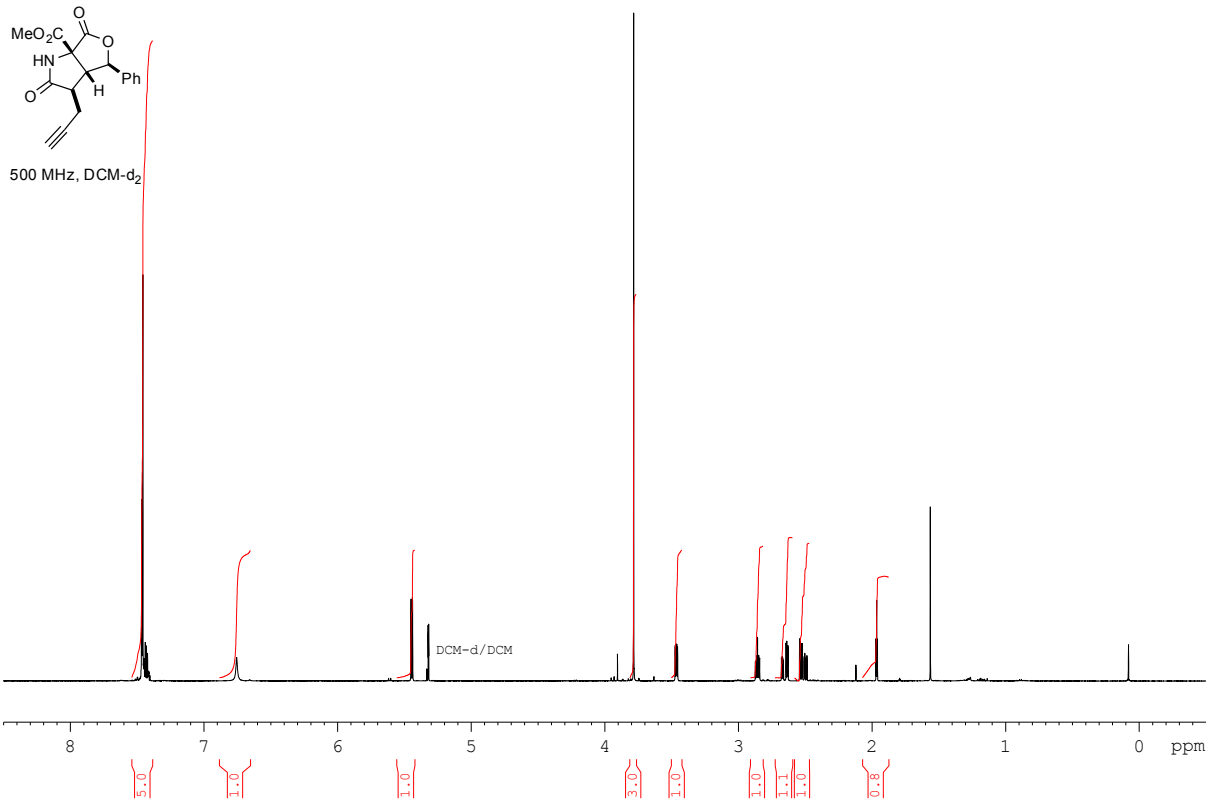


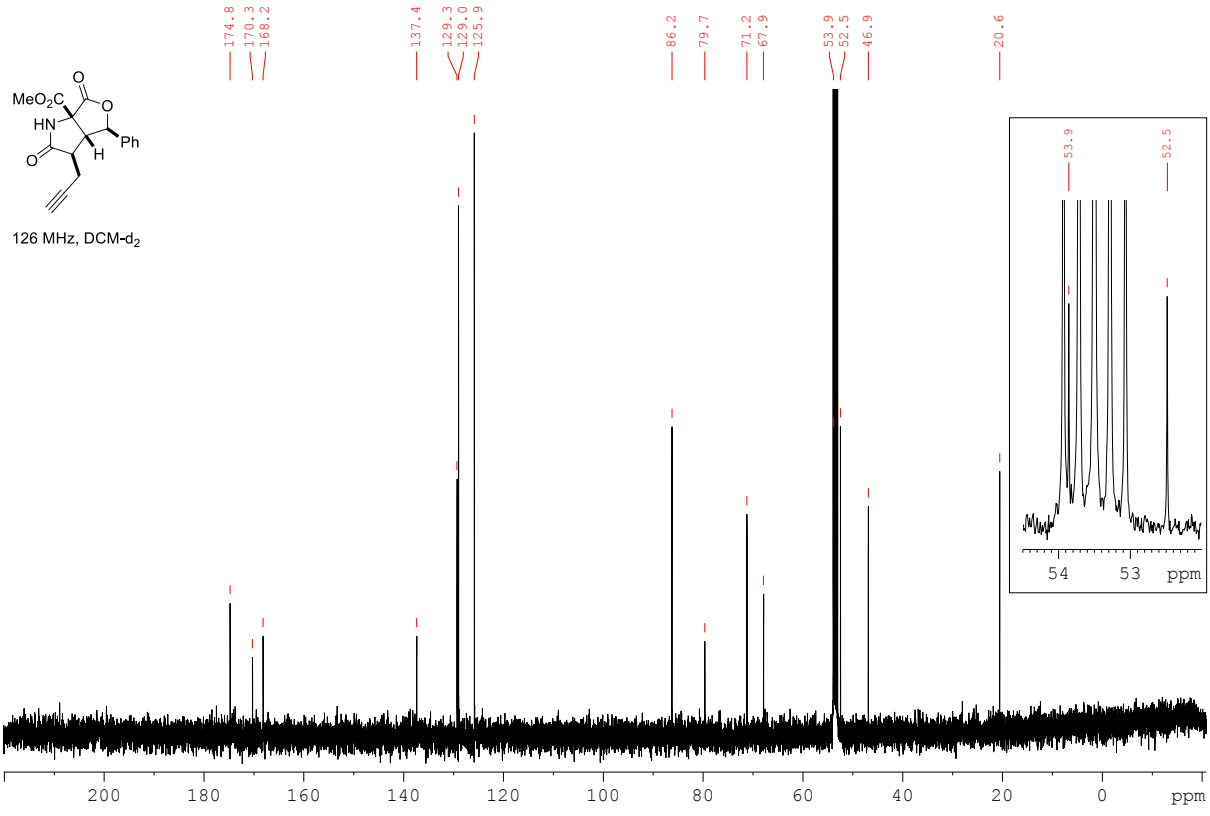
Spectra for compound **10d** (12:1 mixture of diastereomers)



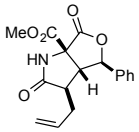


Spectra for compound **10e**

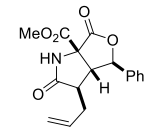




Spectra for compound **10f**

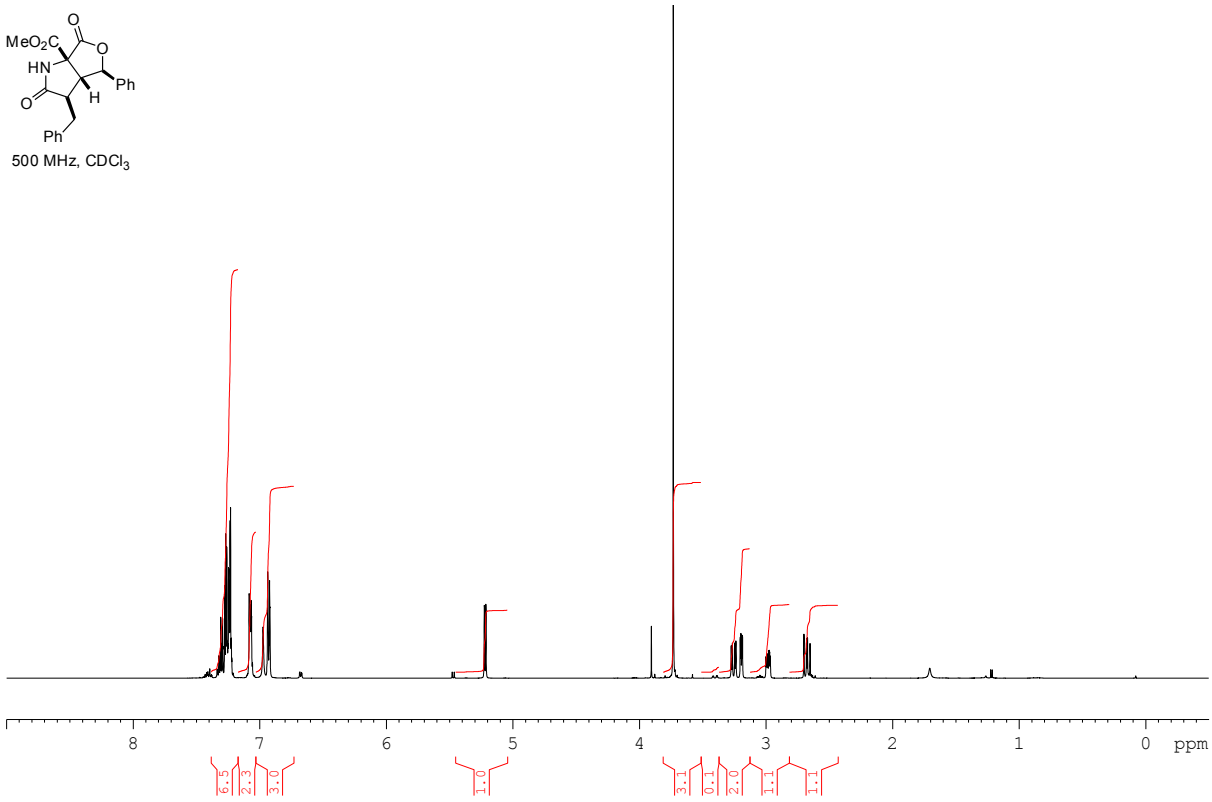


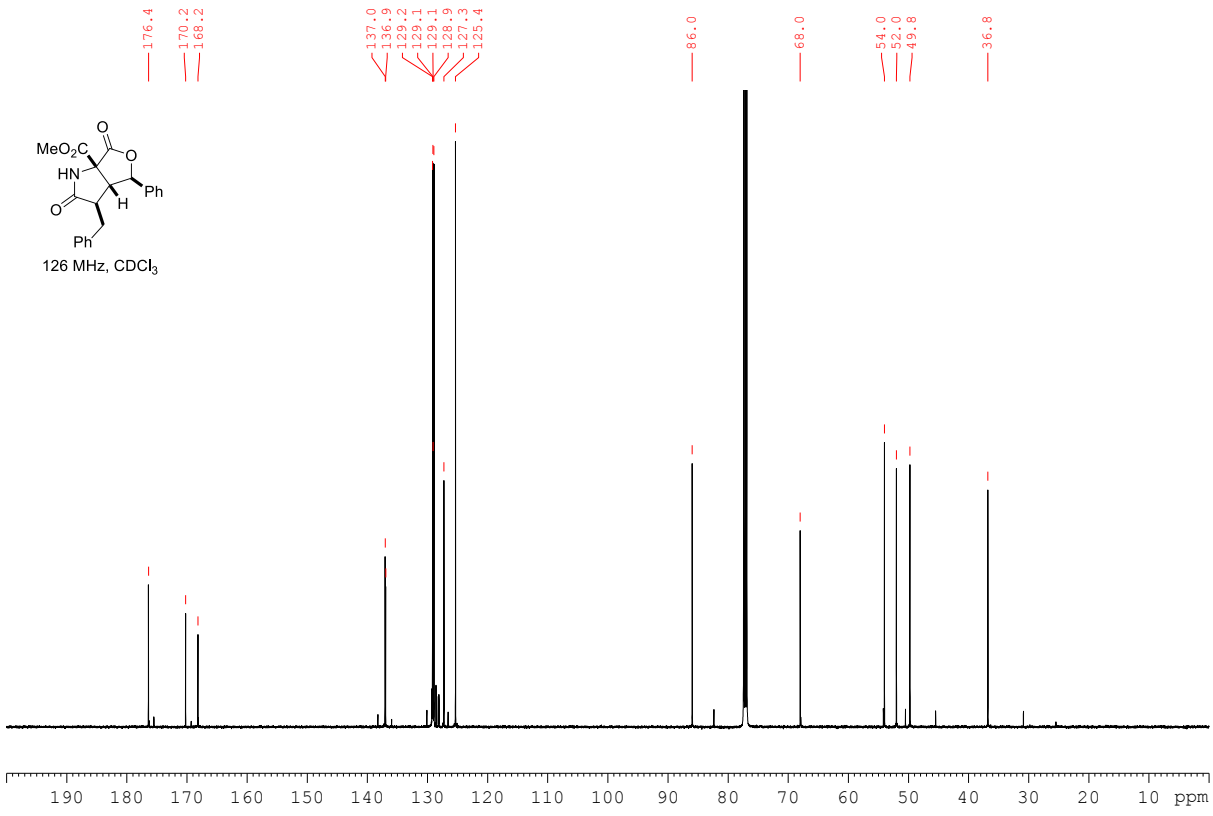
500 MHz, $CDCl_3$



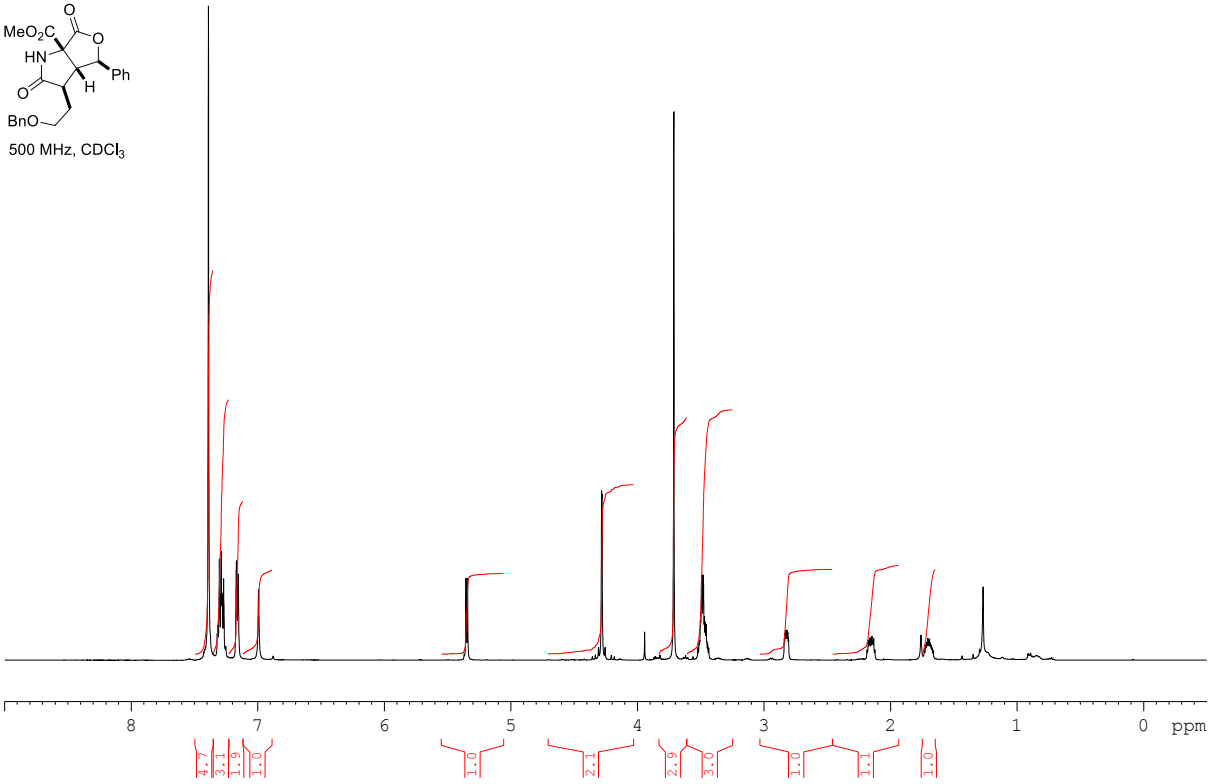
126 MHz, $CDCl_3$

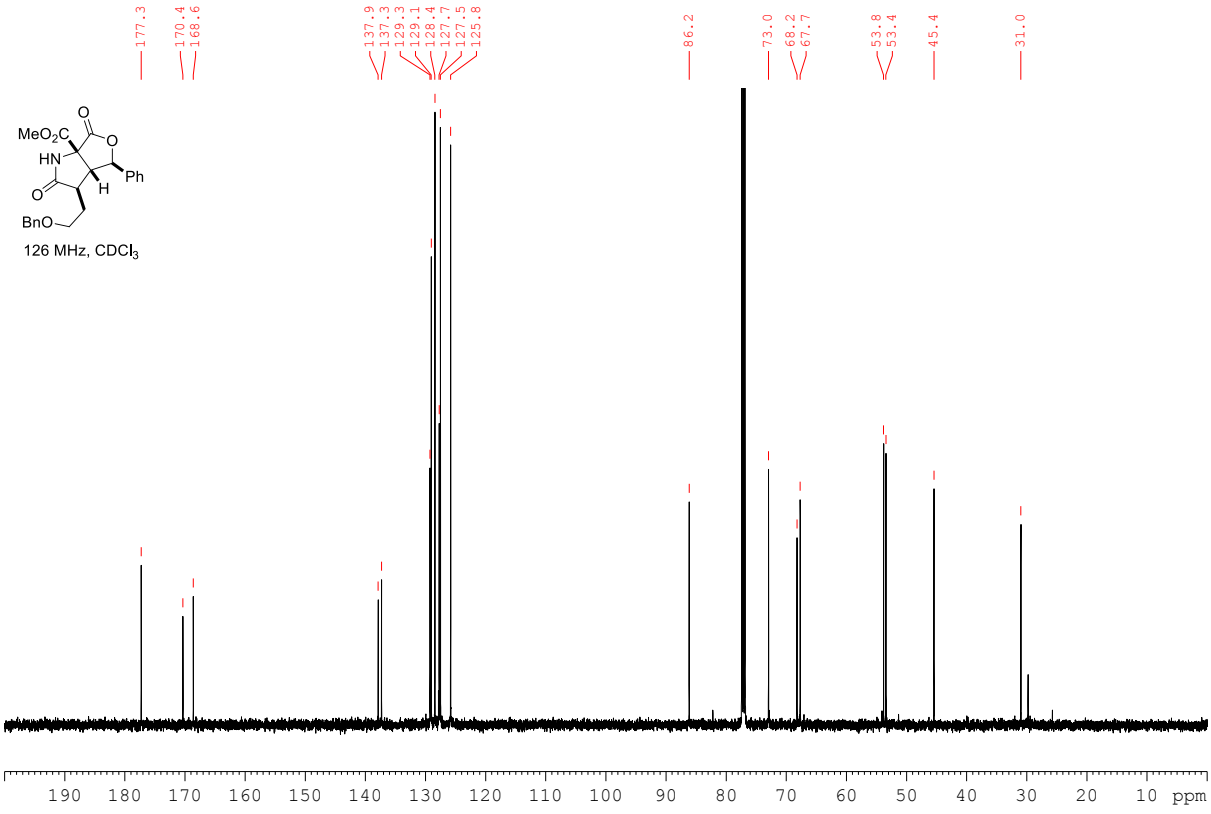
Spectra for compound **10g** (14:1 mixture of diastereomers)



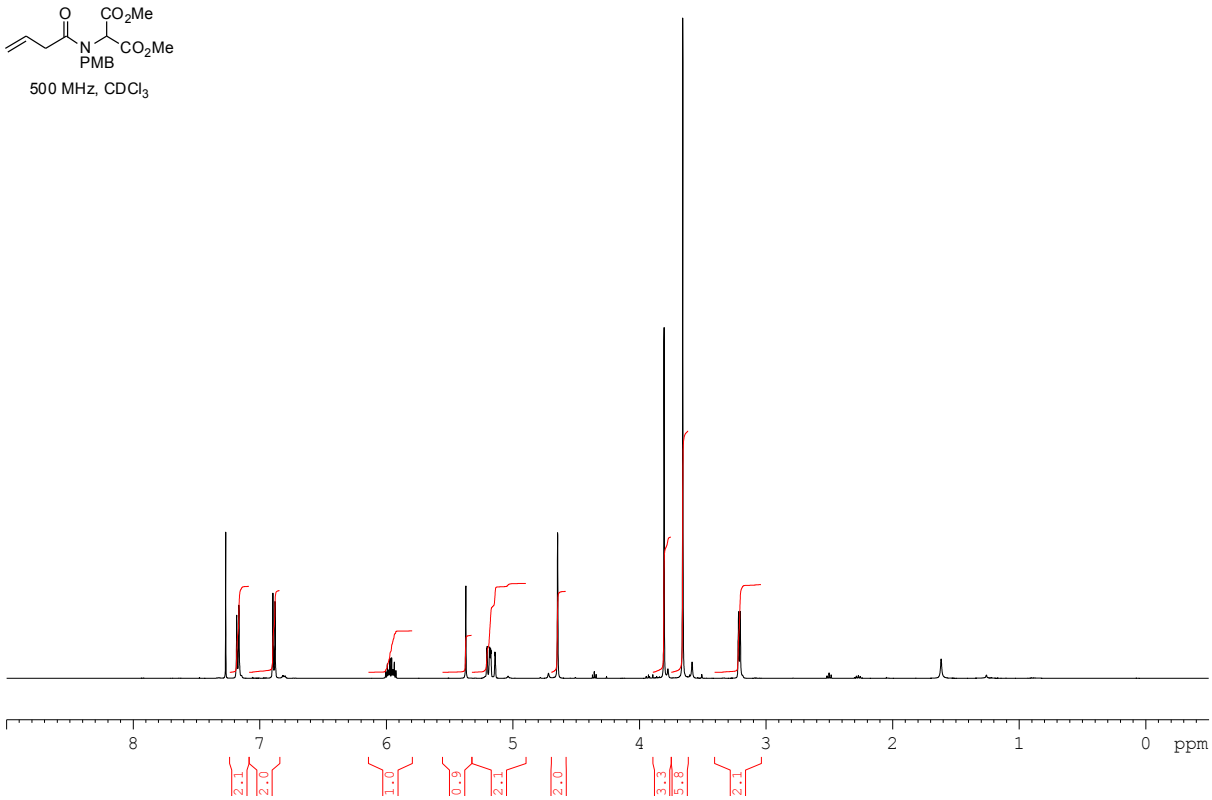


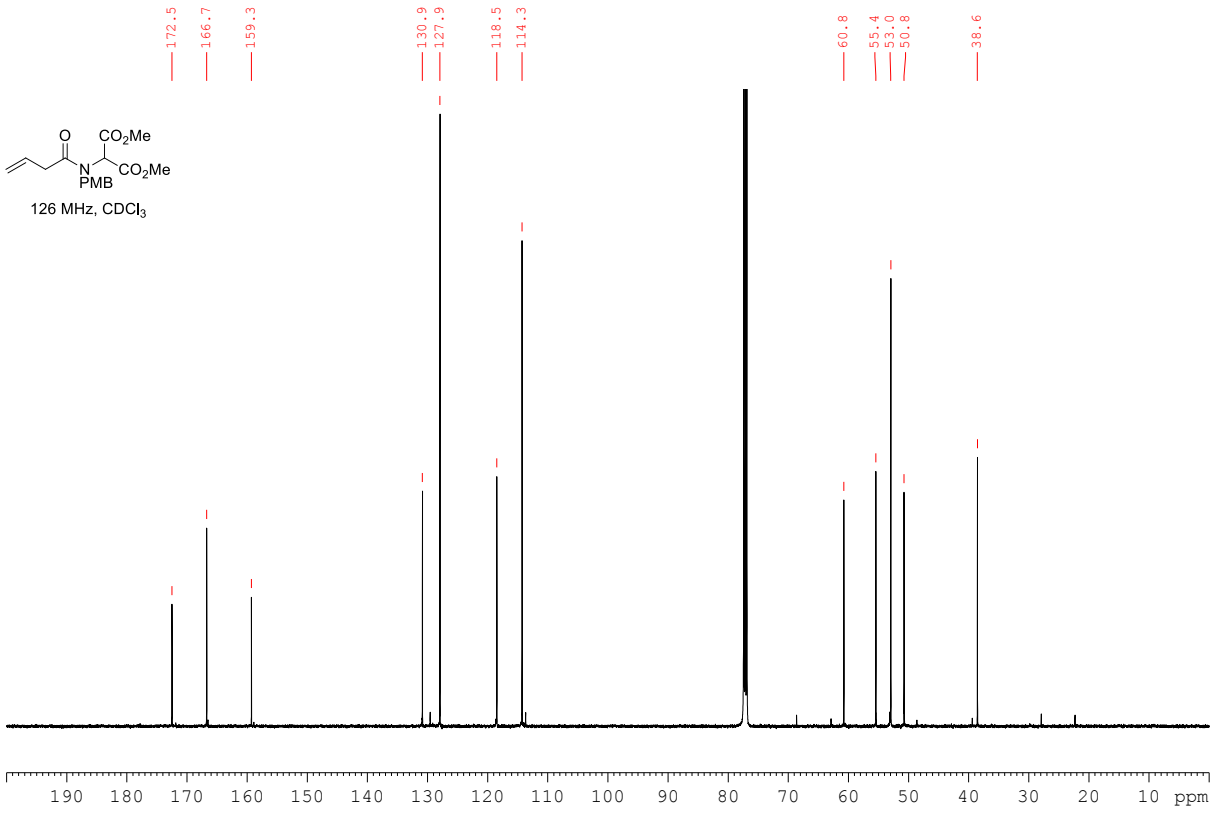
Spectra for compound **10h**



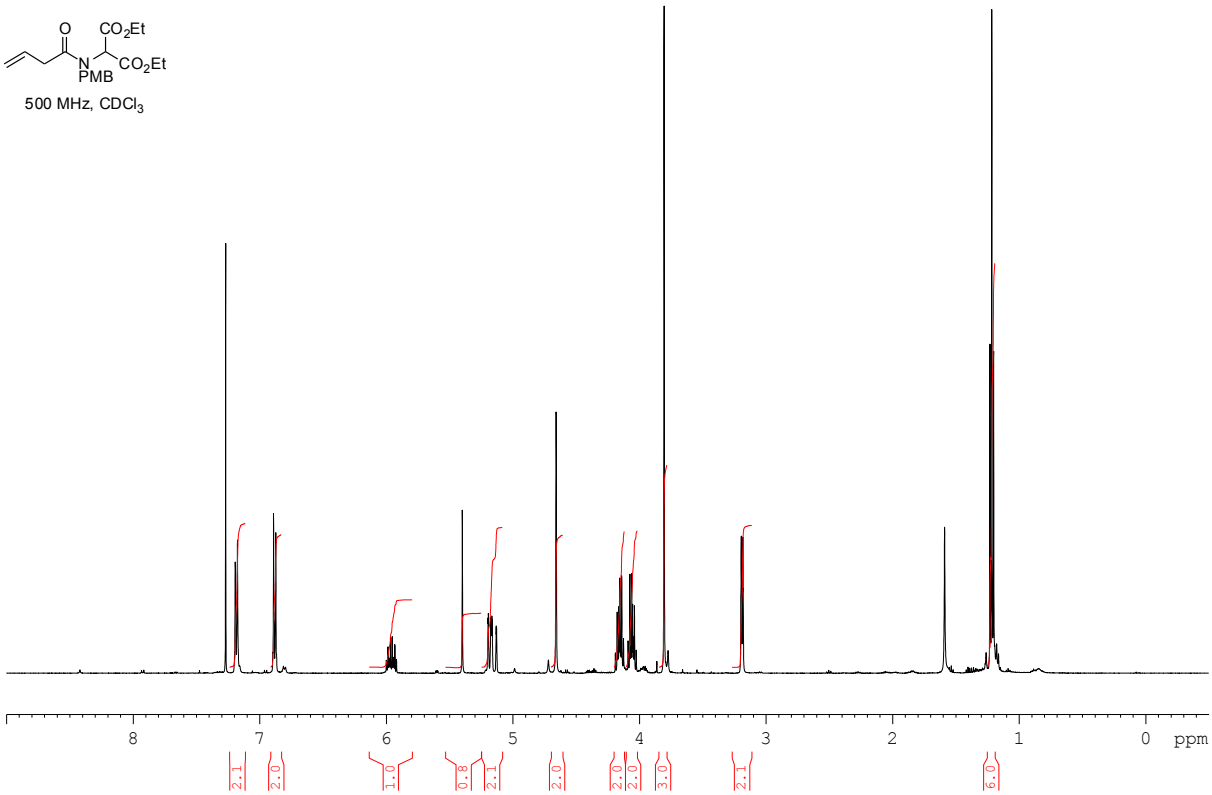


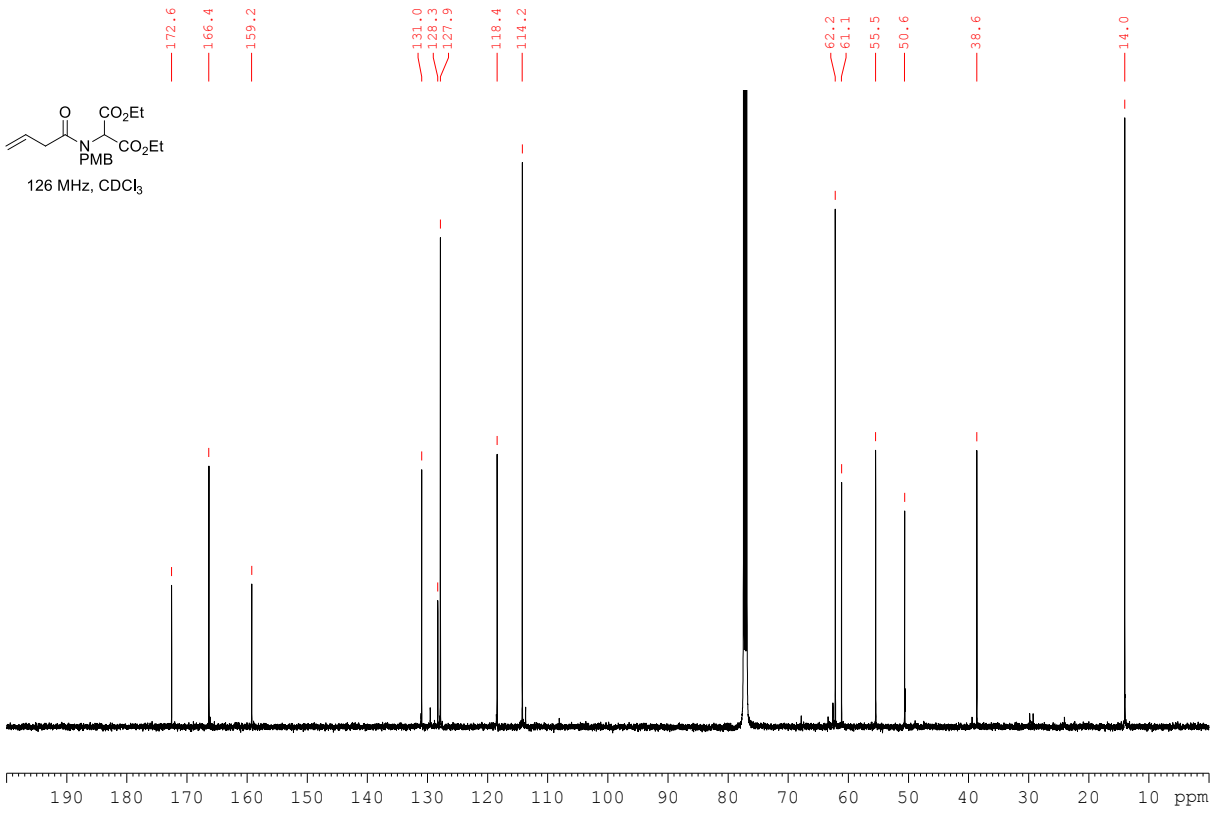
Spectra for compound **11a**



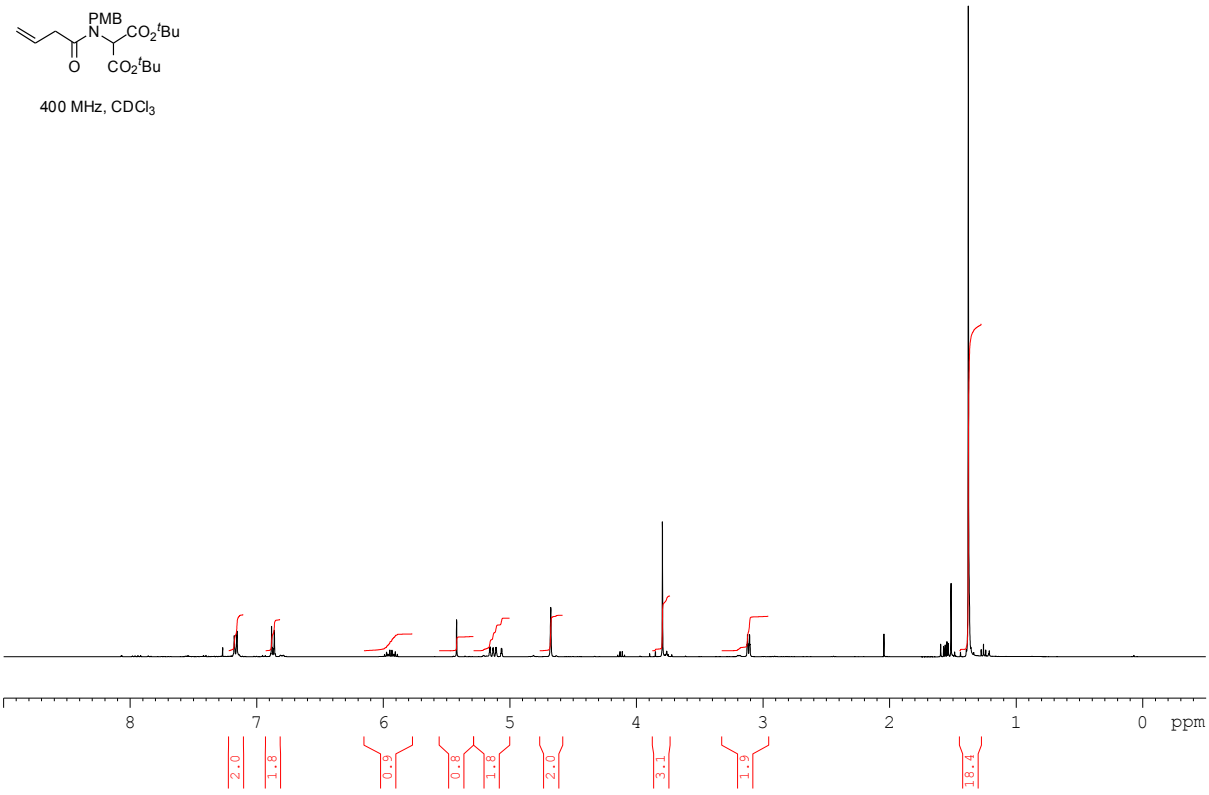


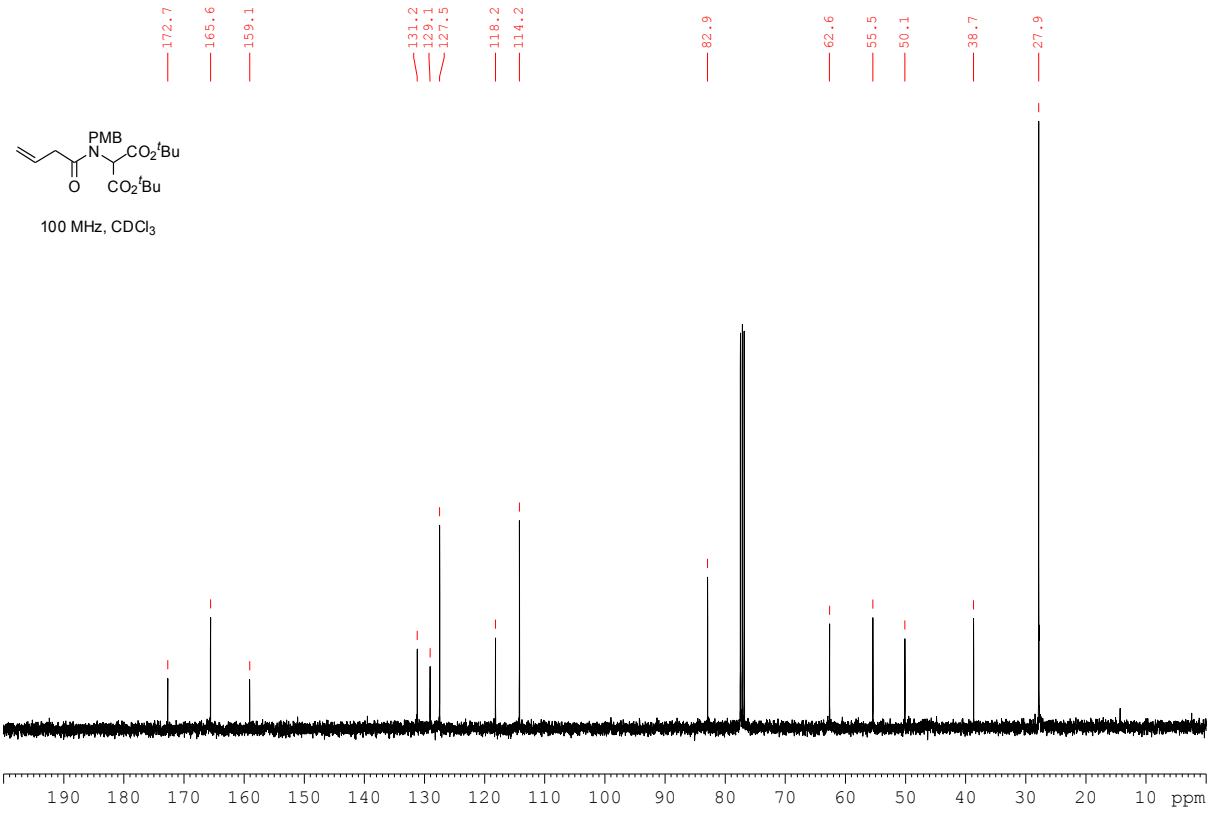
Spectra for compound **11b**



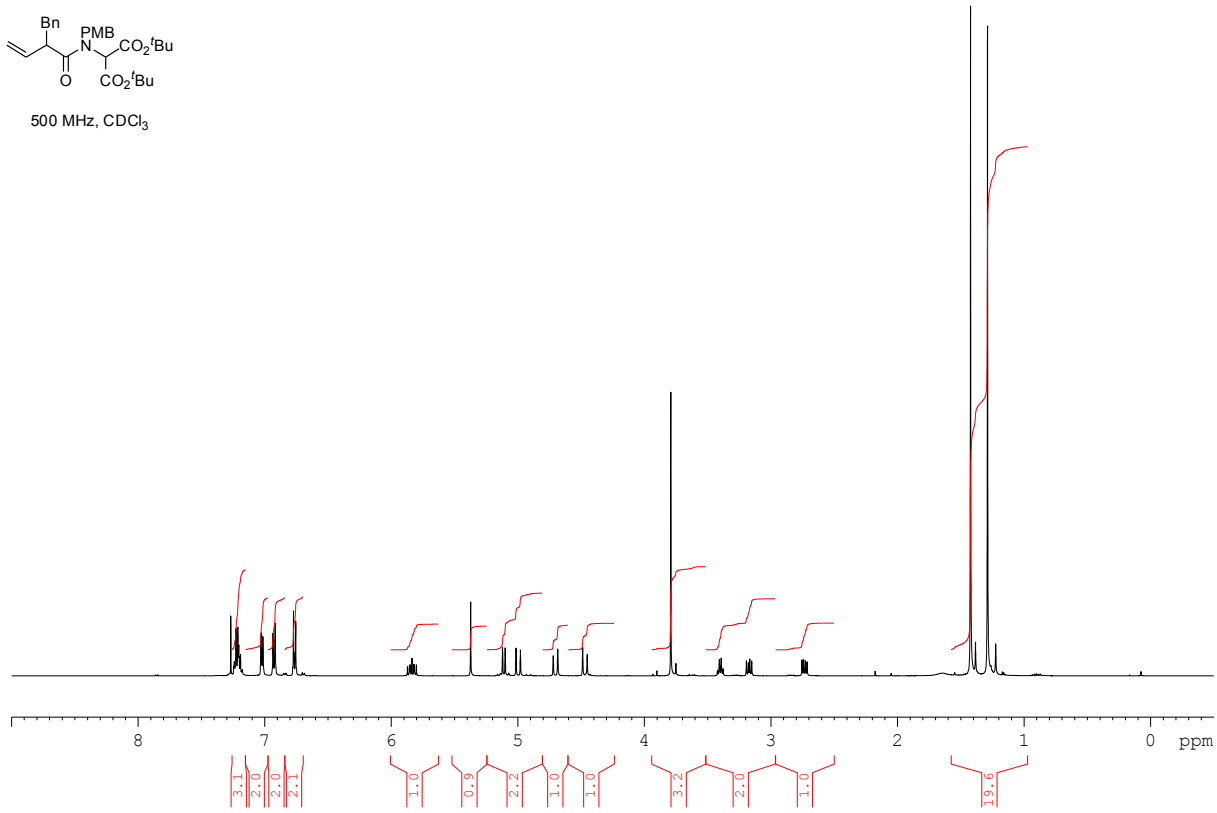


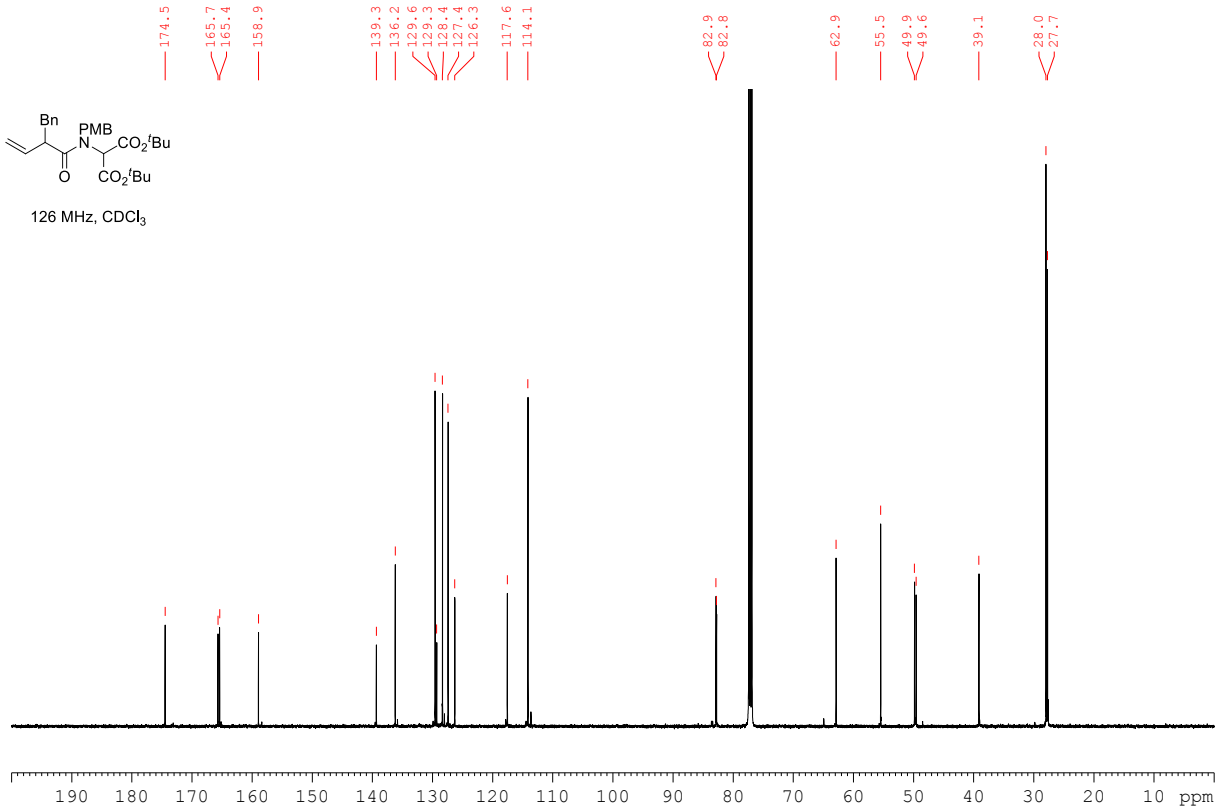
Spectra for compound **11c**



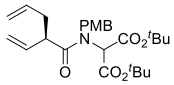


Spectra for compound **11d**

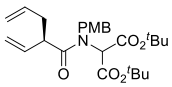




Spectra for compound **(–)-11e**

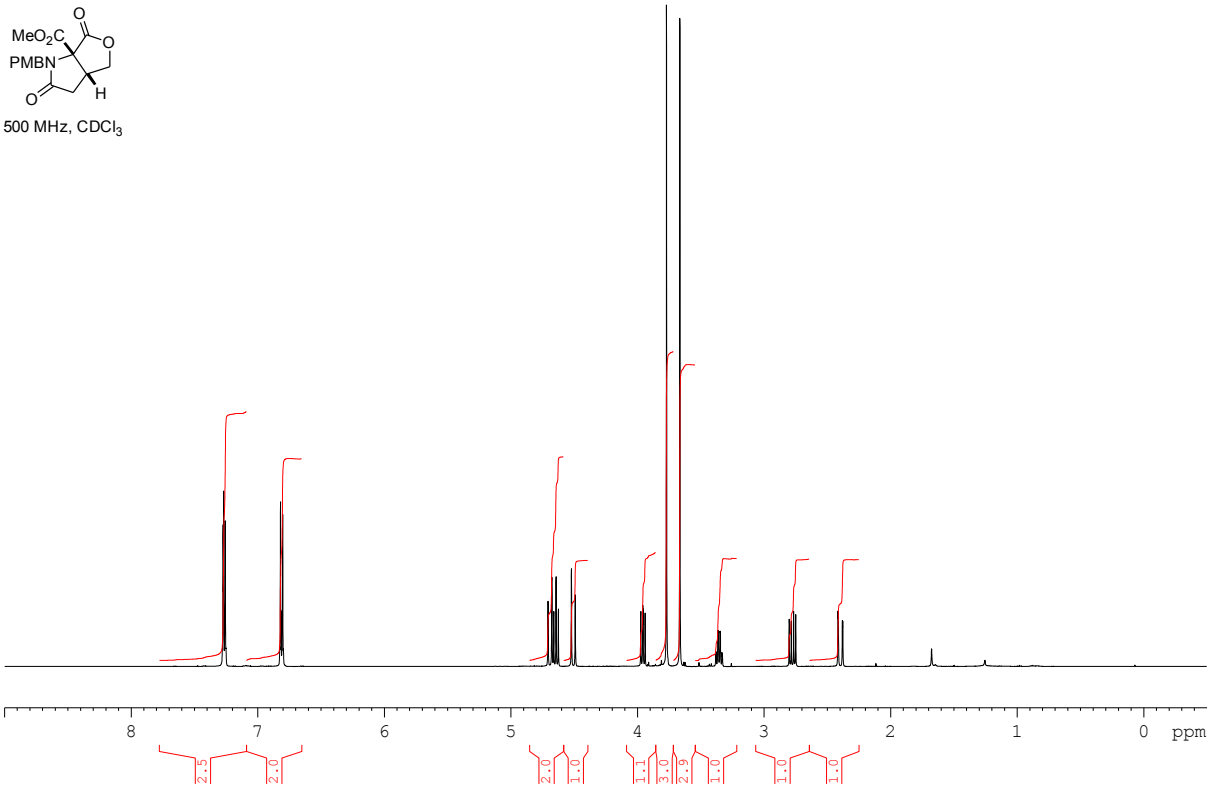


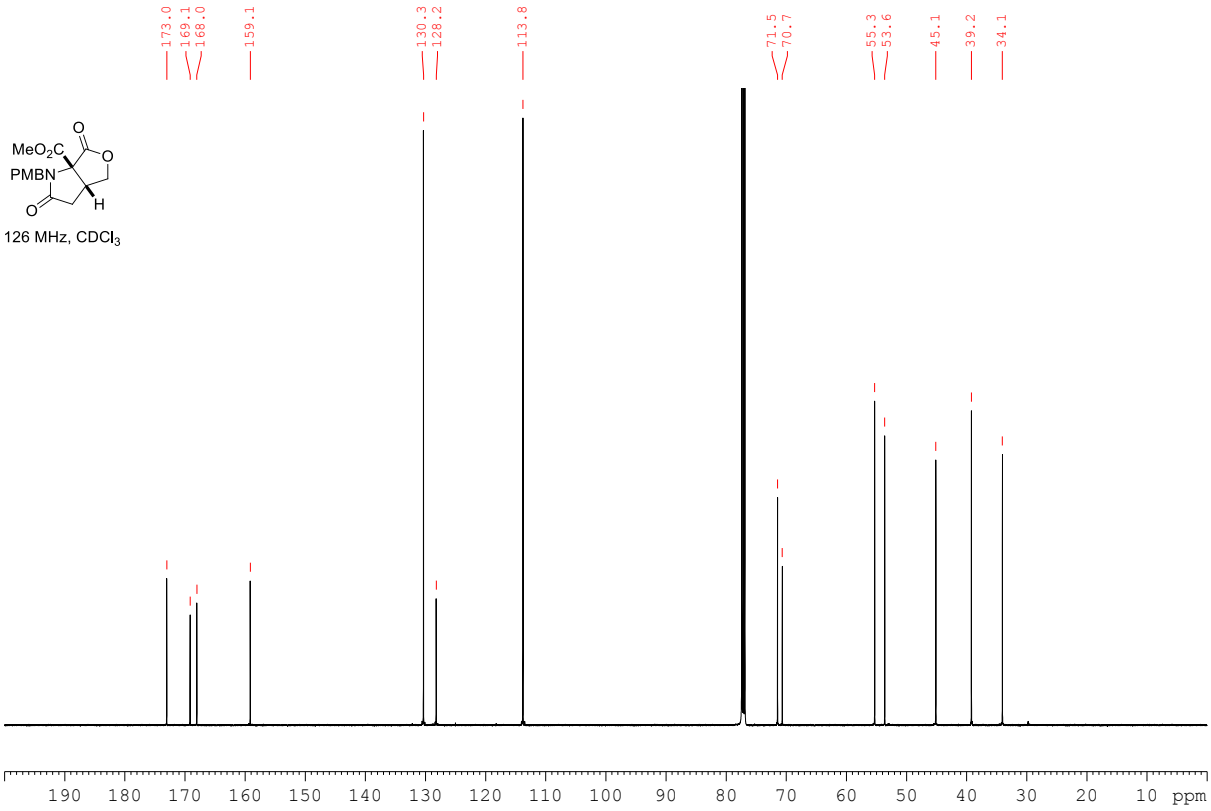
500 MHz, $CDCl_3$



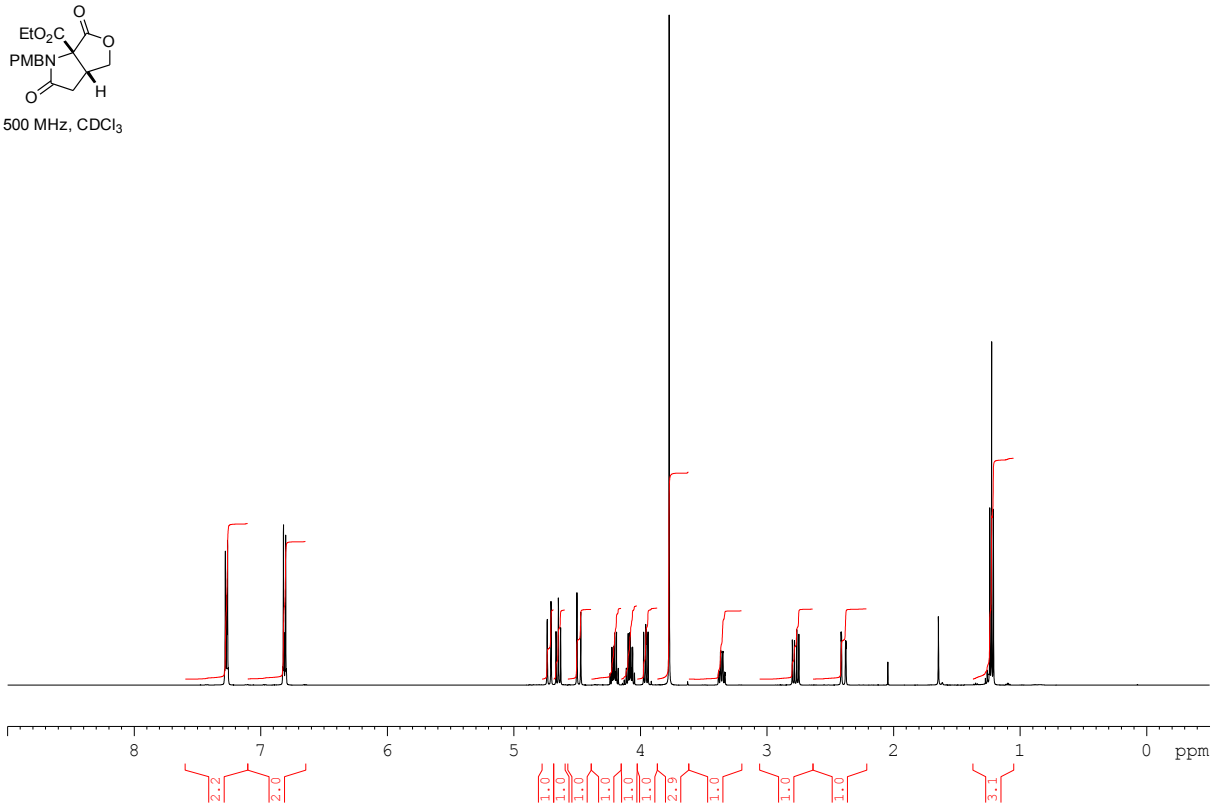
126 MHz, $CDCl_3$

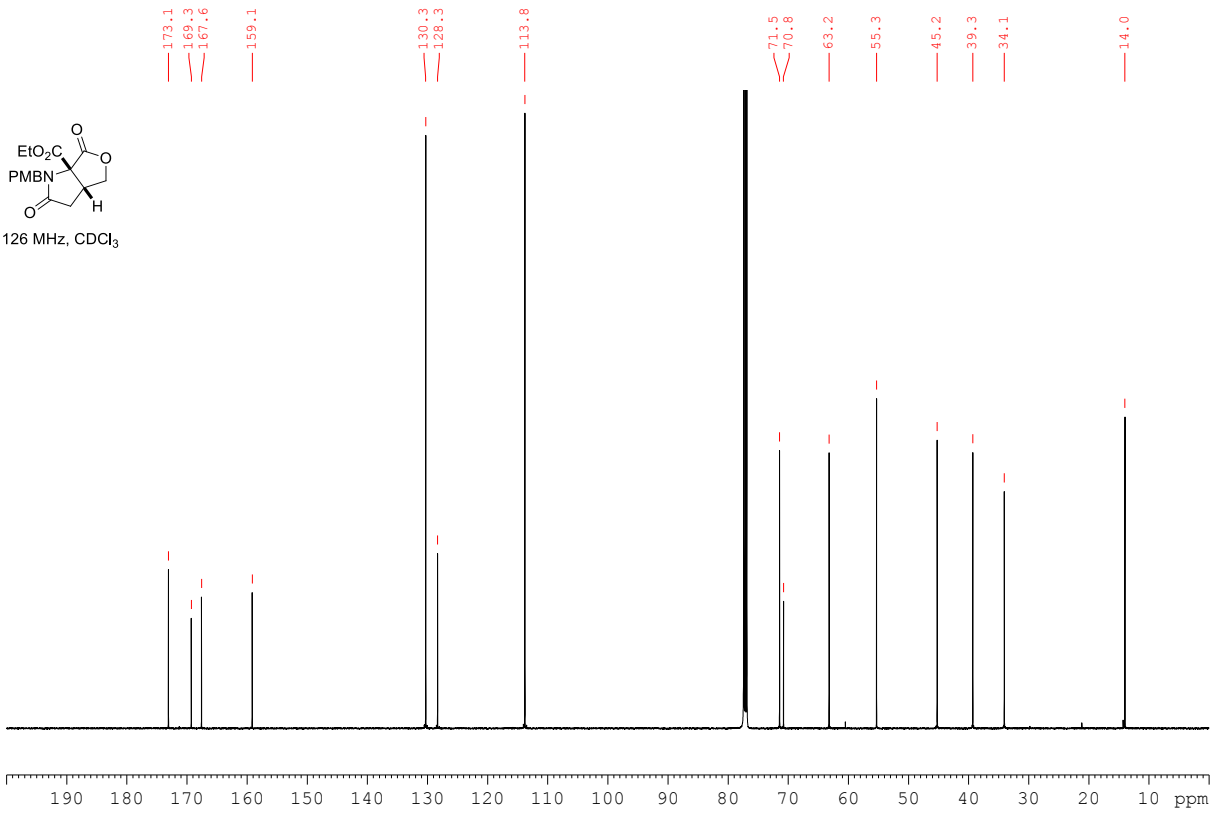
Spectra for compound **12a**



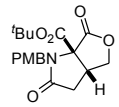


Spectra for compound **12b**

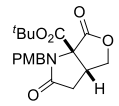




Spectra for compound **12c**

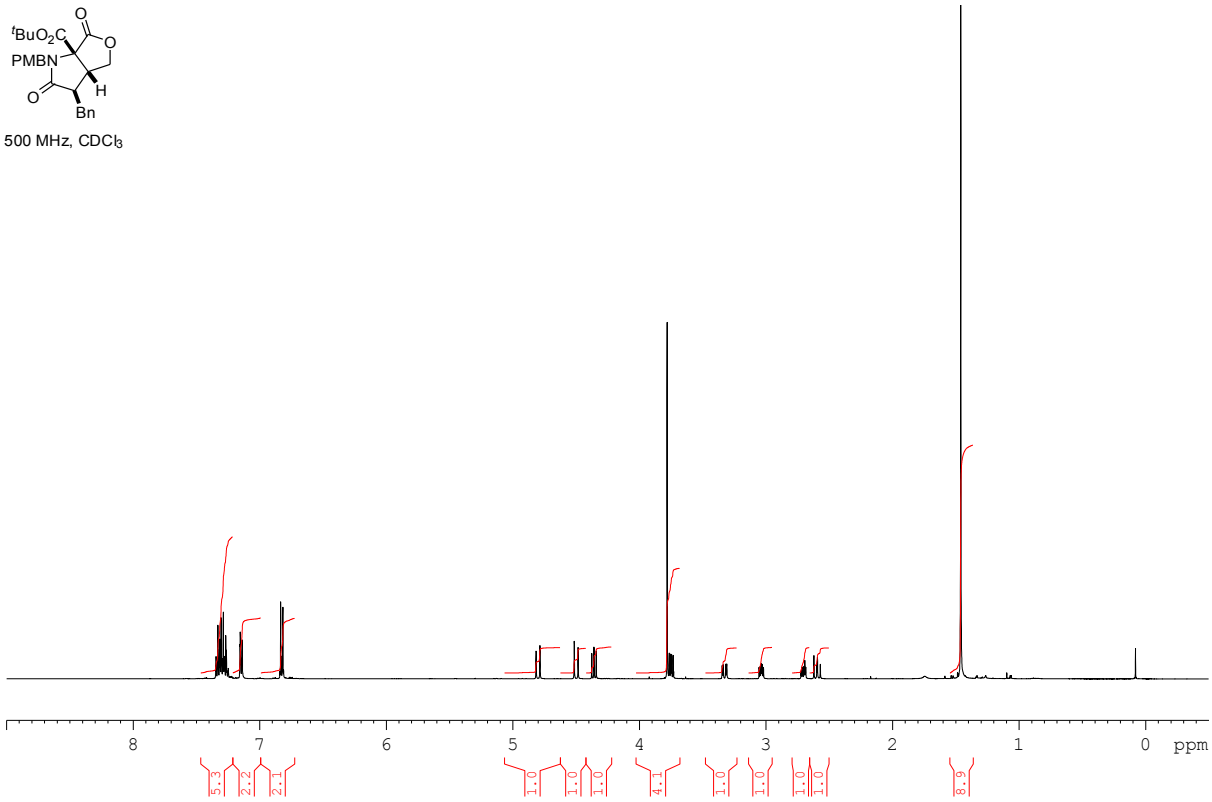


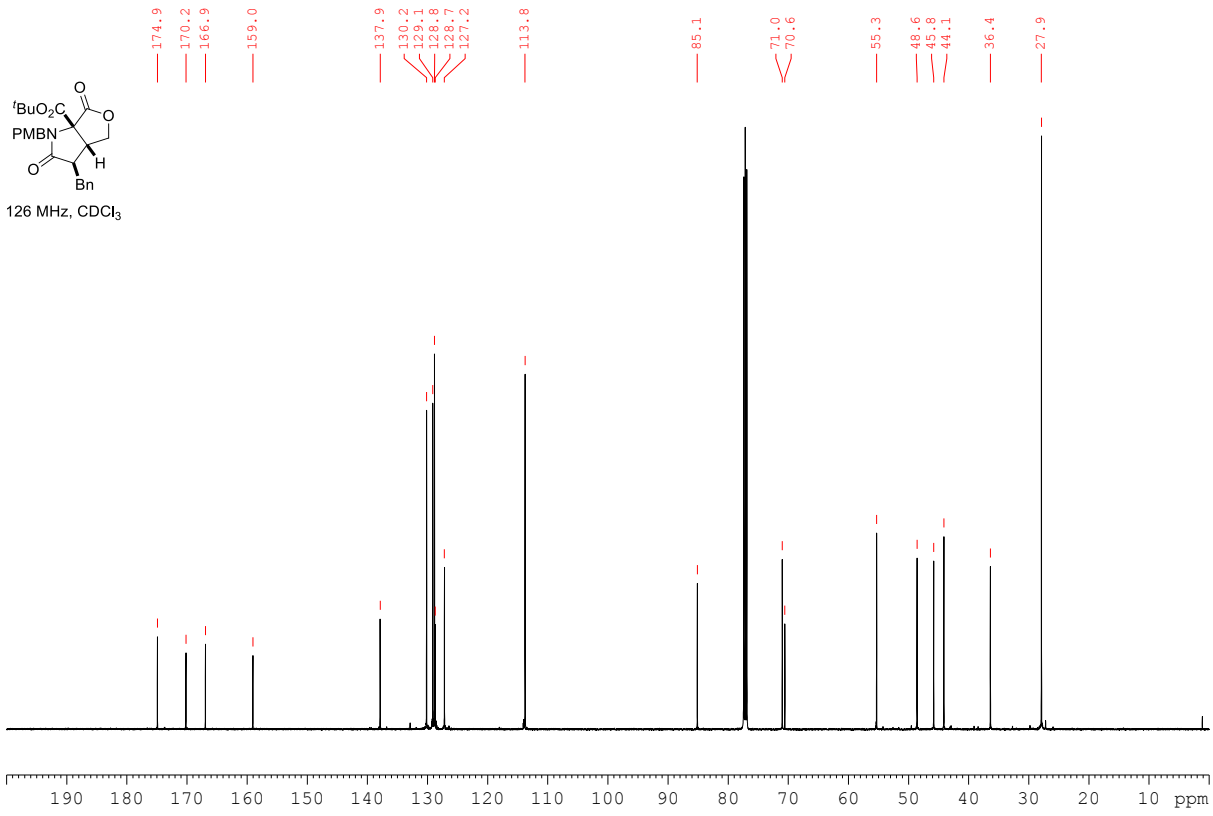
500 MHz, $CDCl_3$



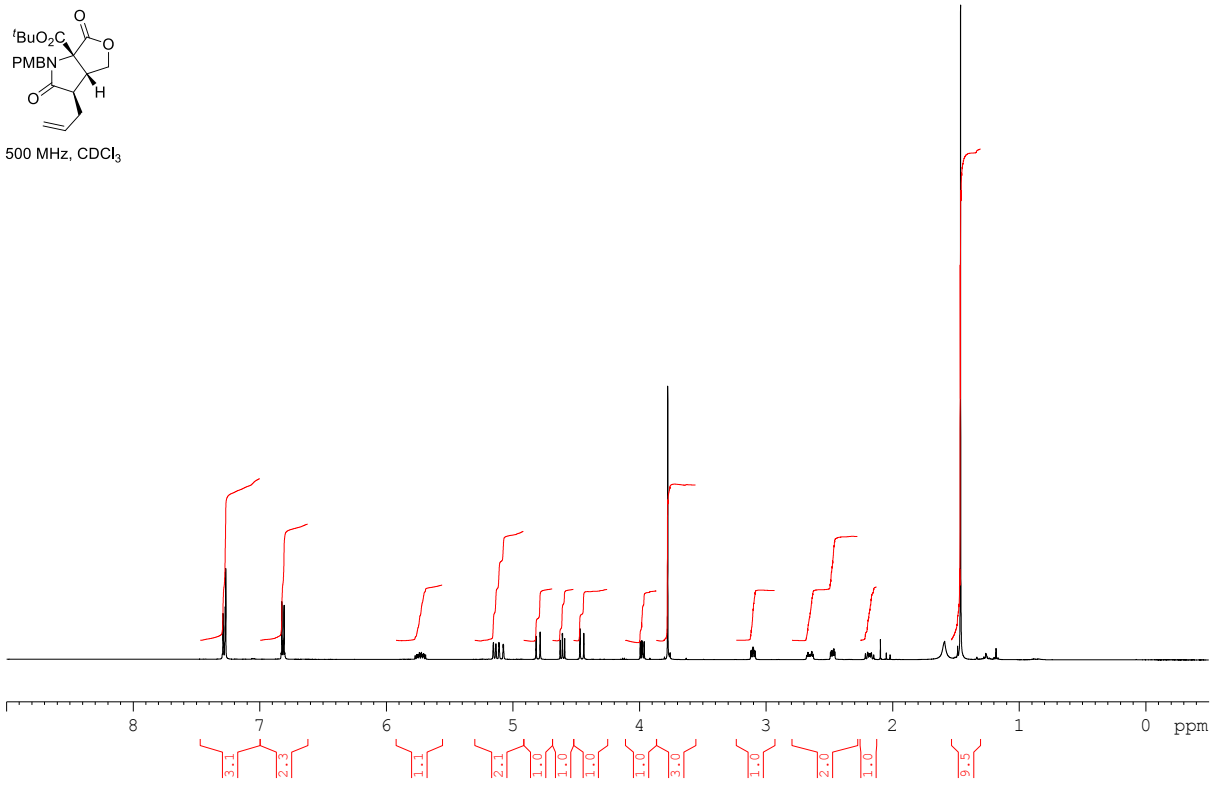
126 MHz, $CDCl_3$

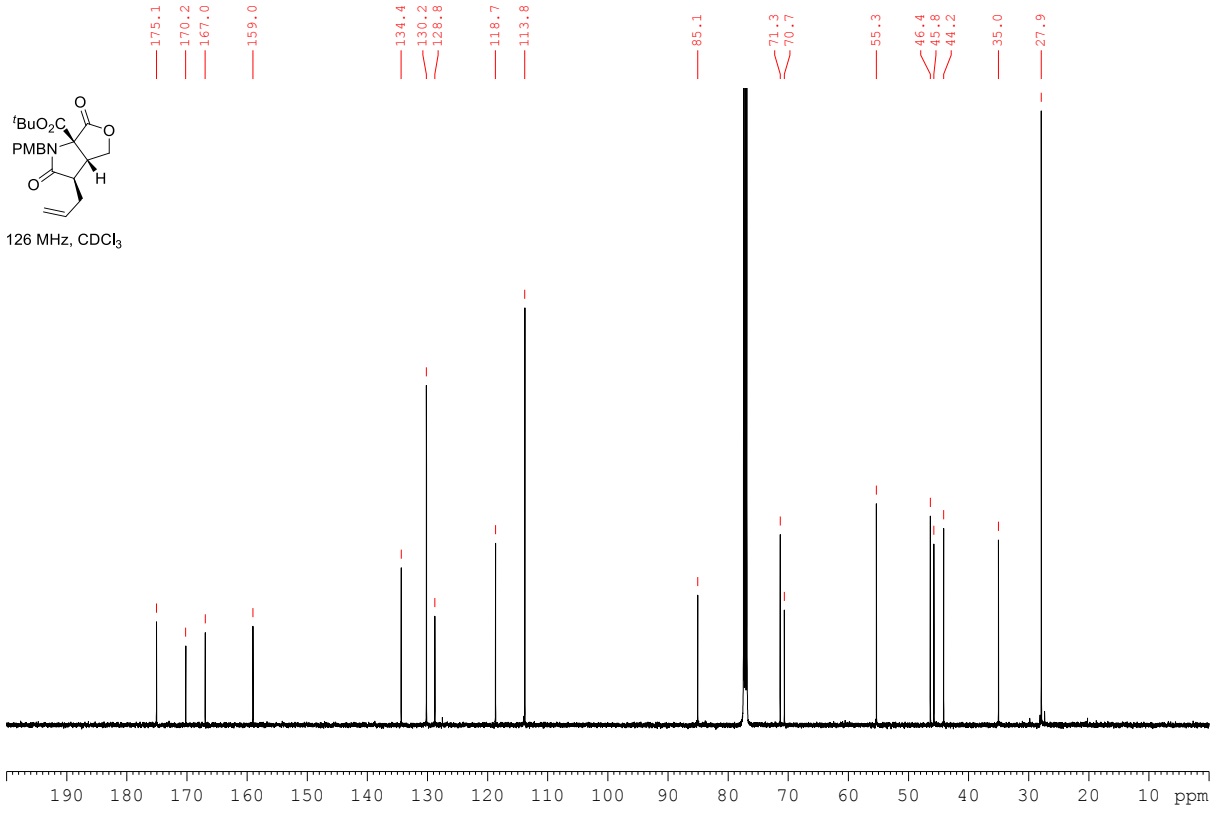
Spectra for compound **12d**



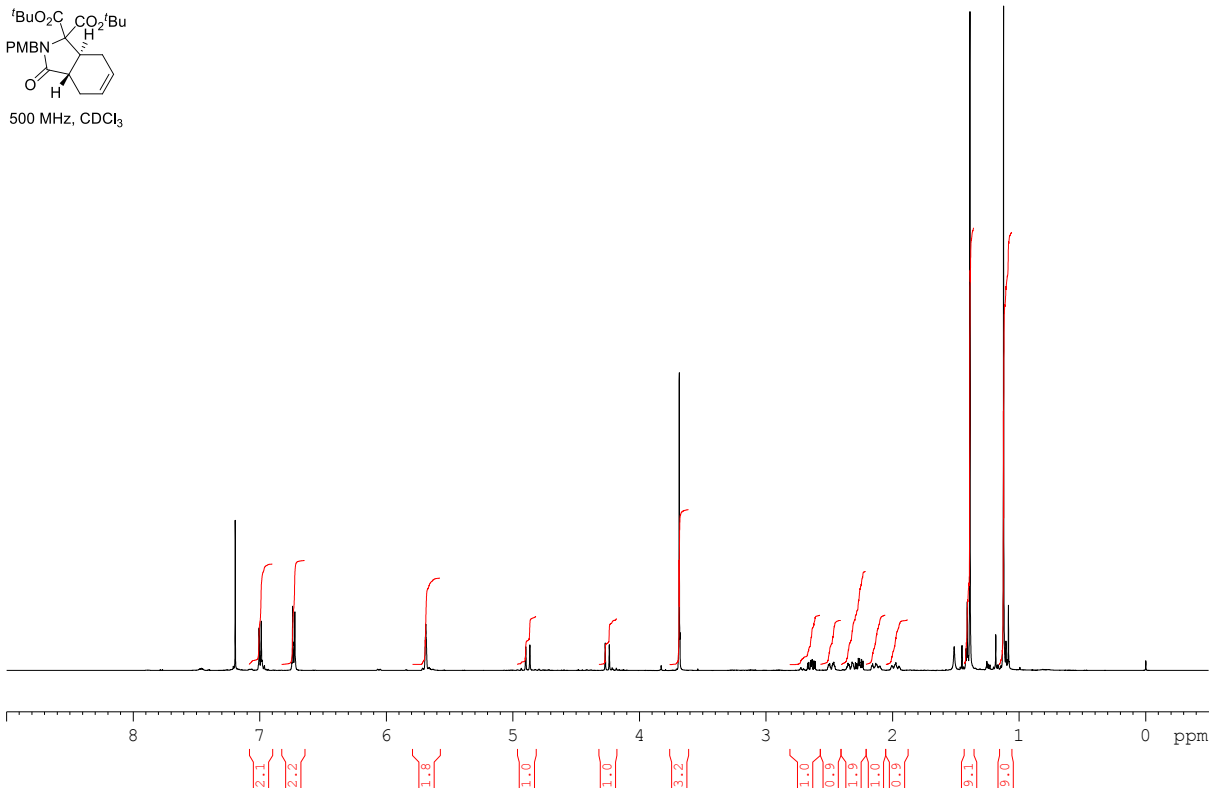


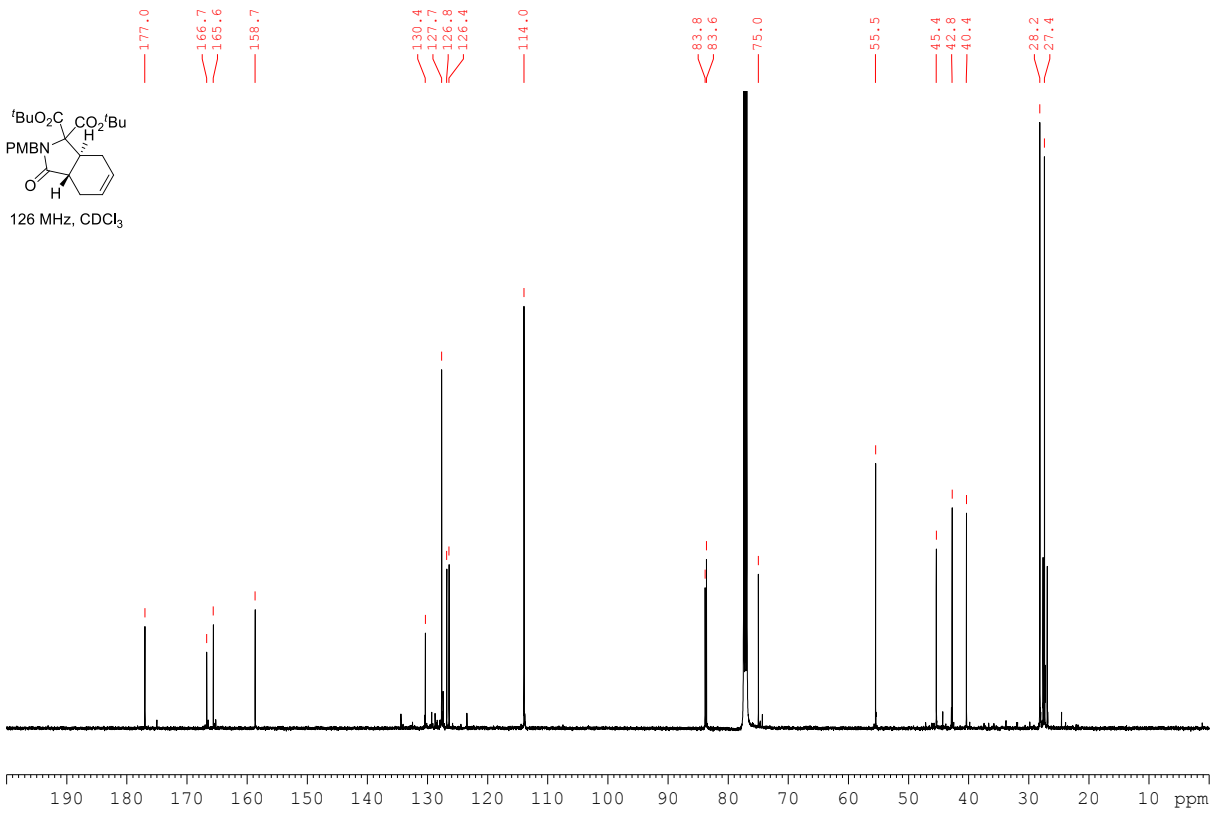
Spectra for compound **(+)-12e**



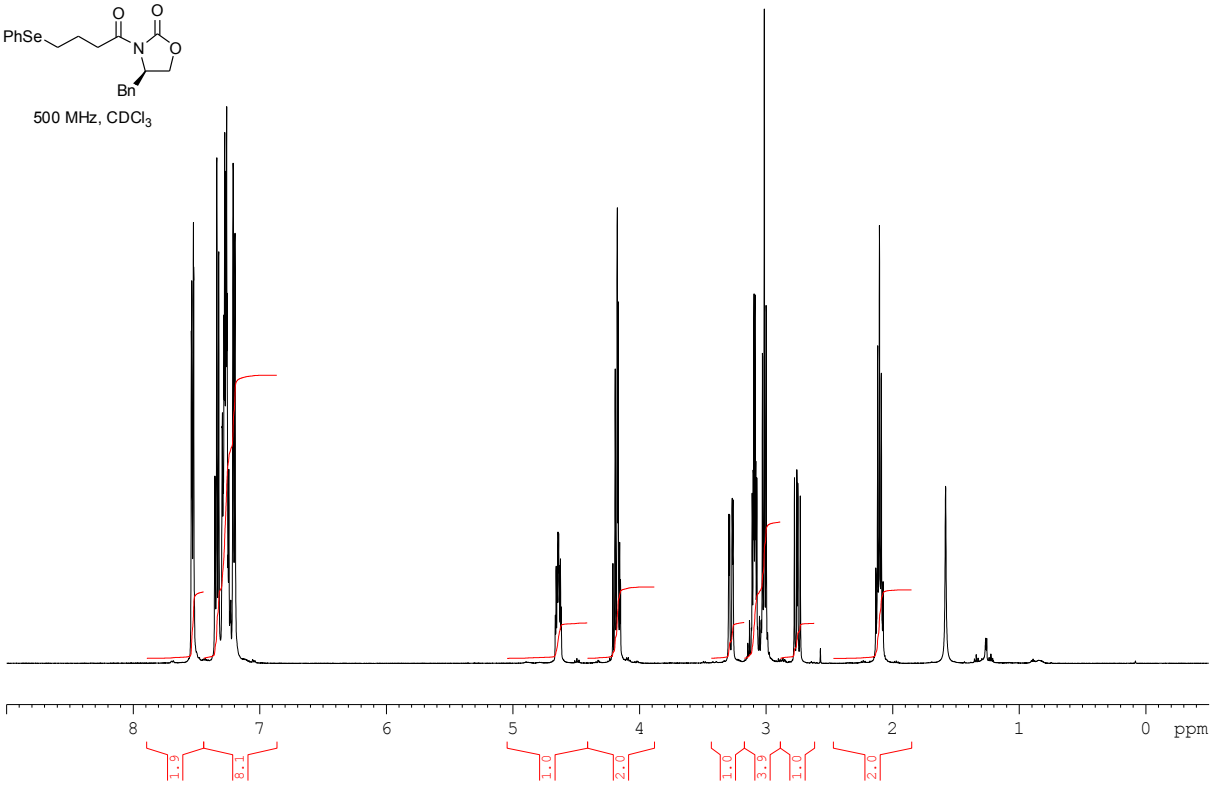


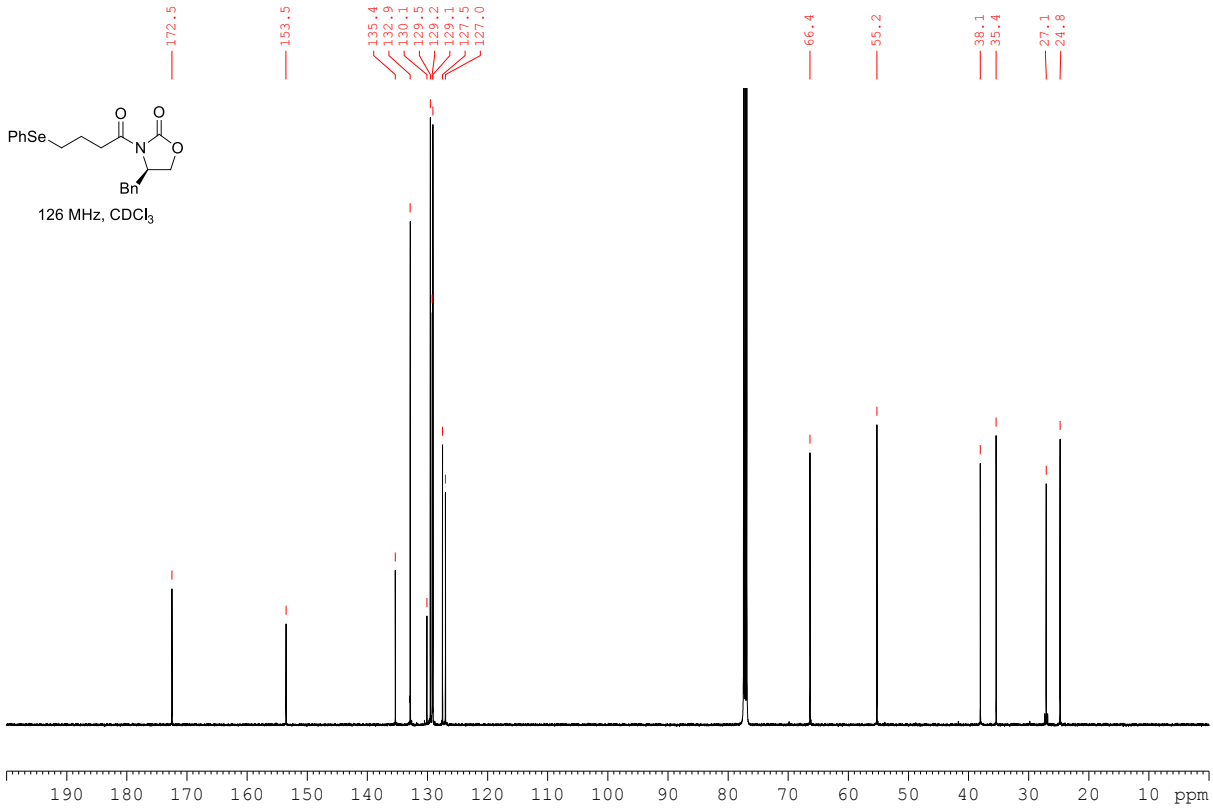
Spectra for compound (–)-**16**



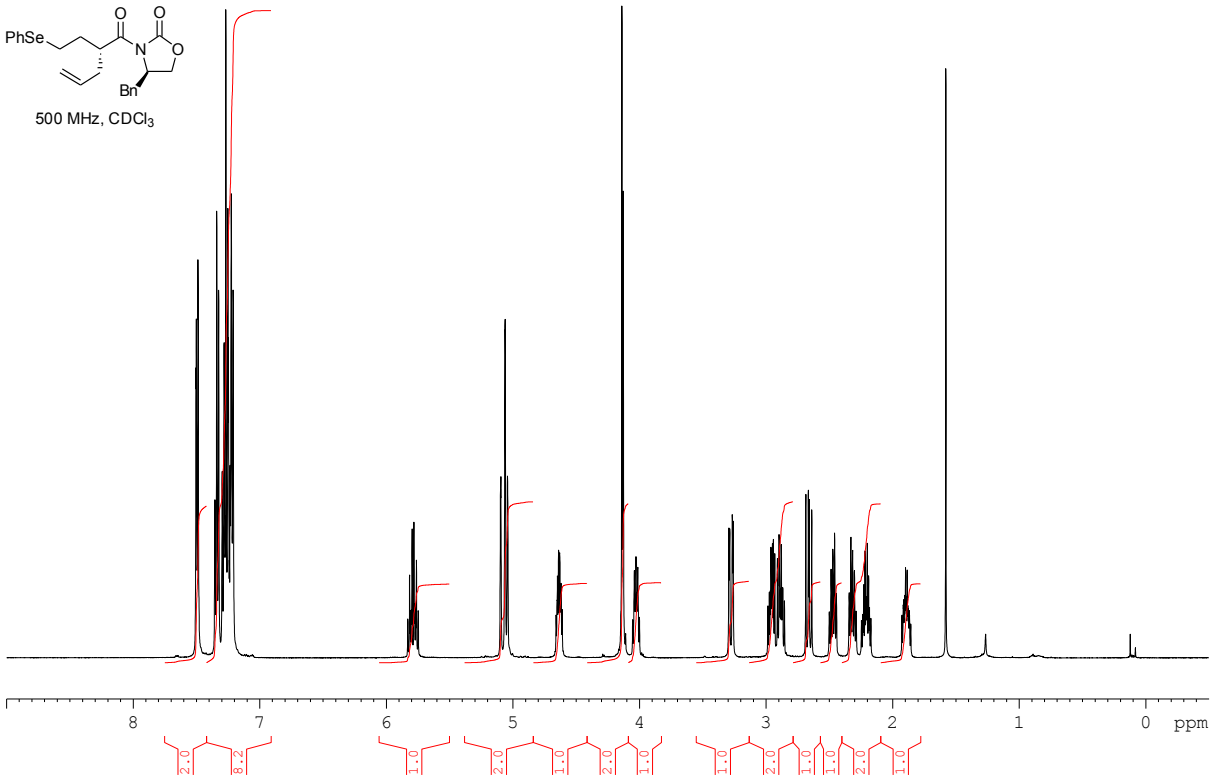


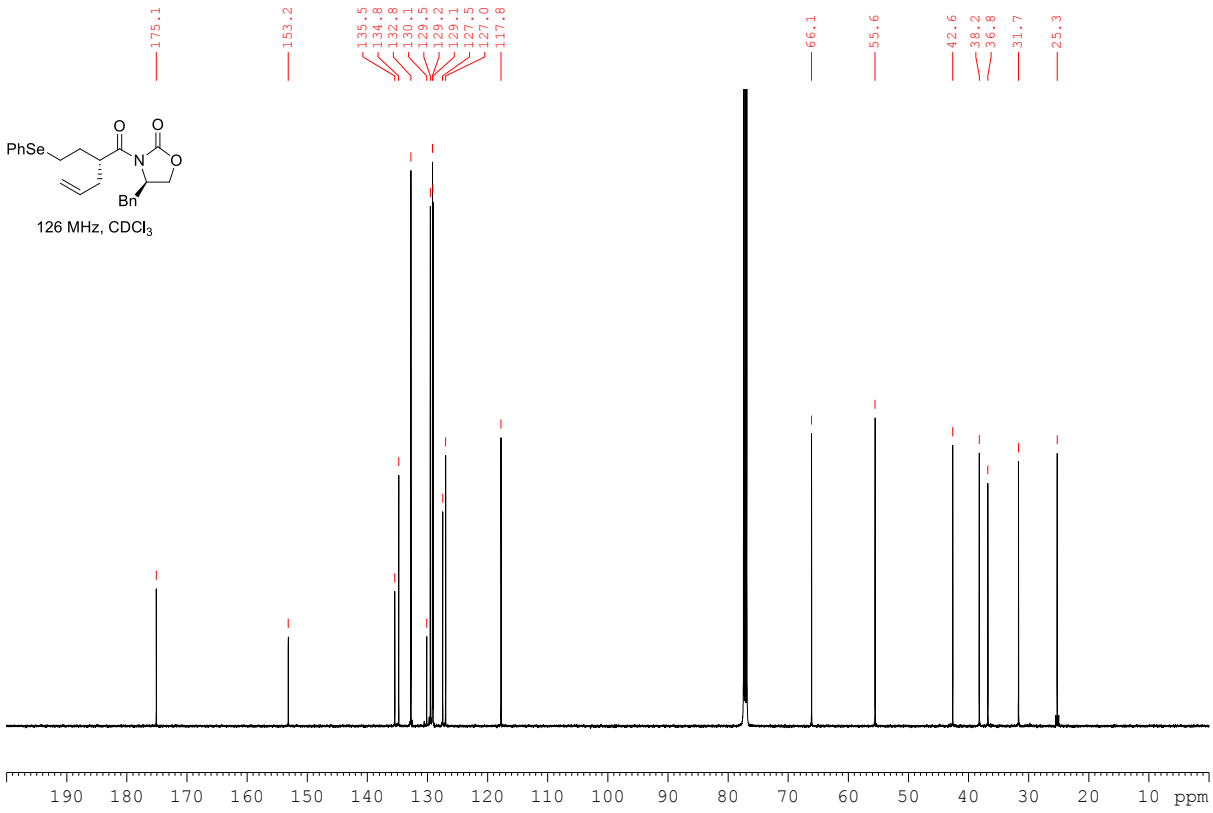
Spectra for compound **20**



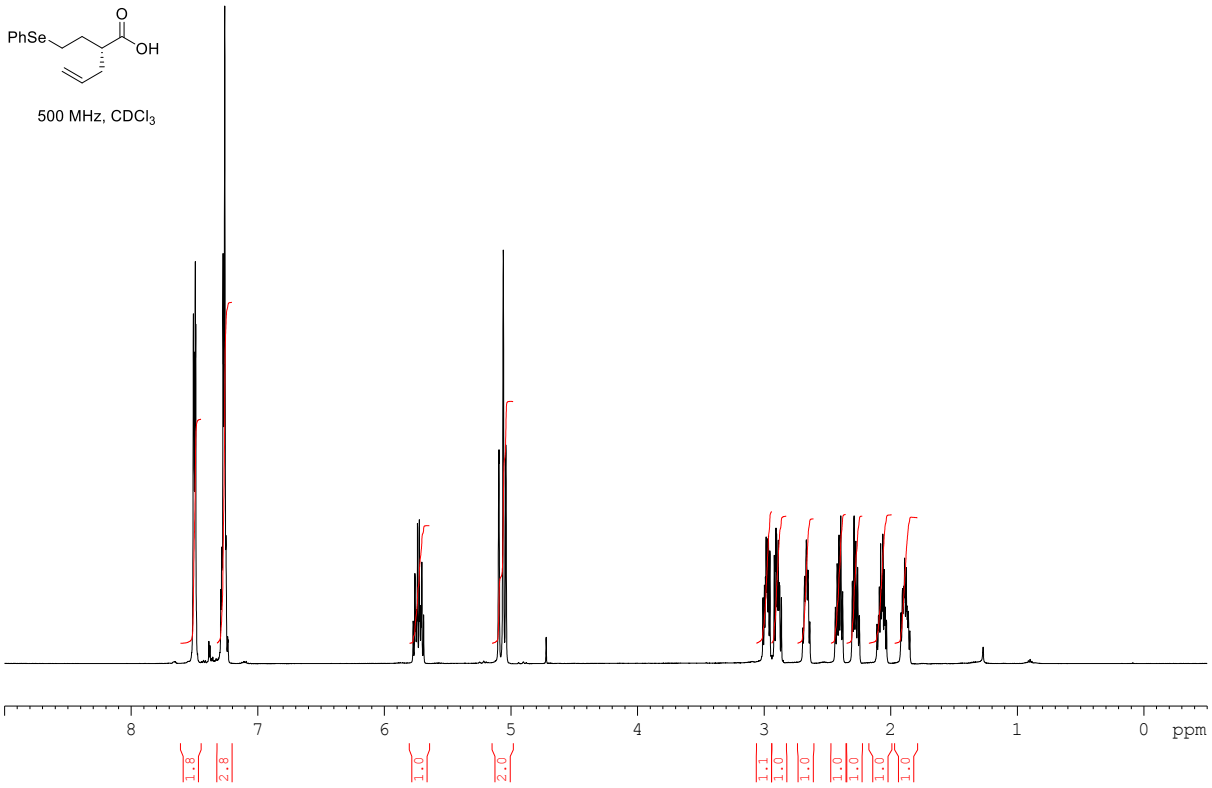


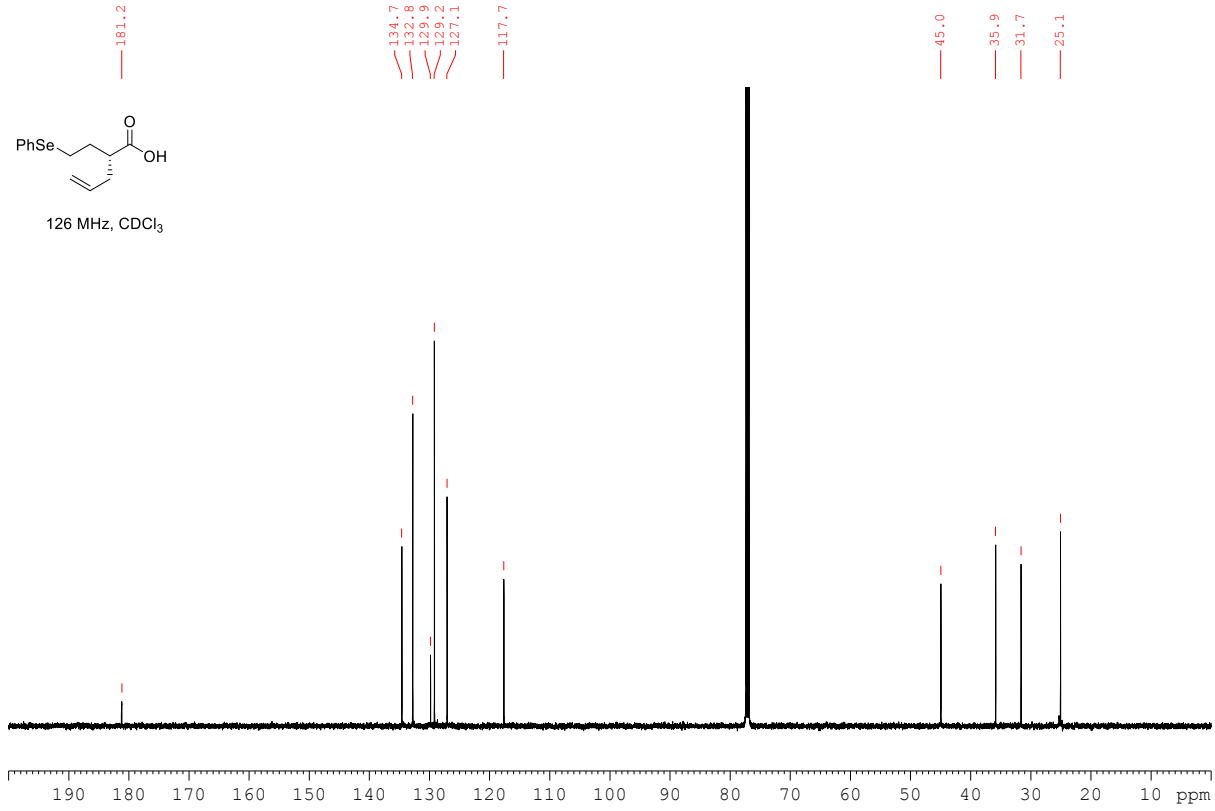
Spectra for compound **21**



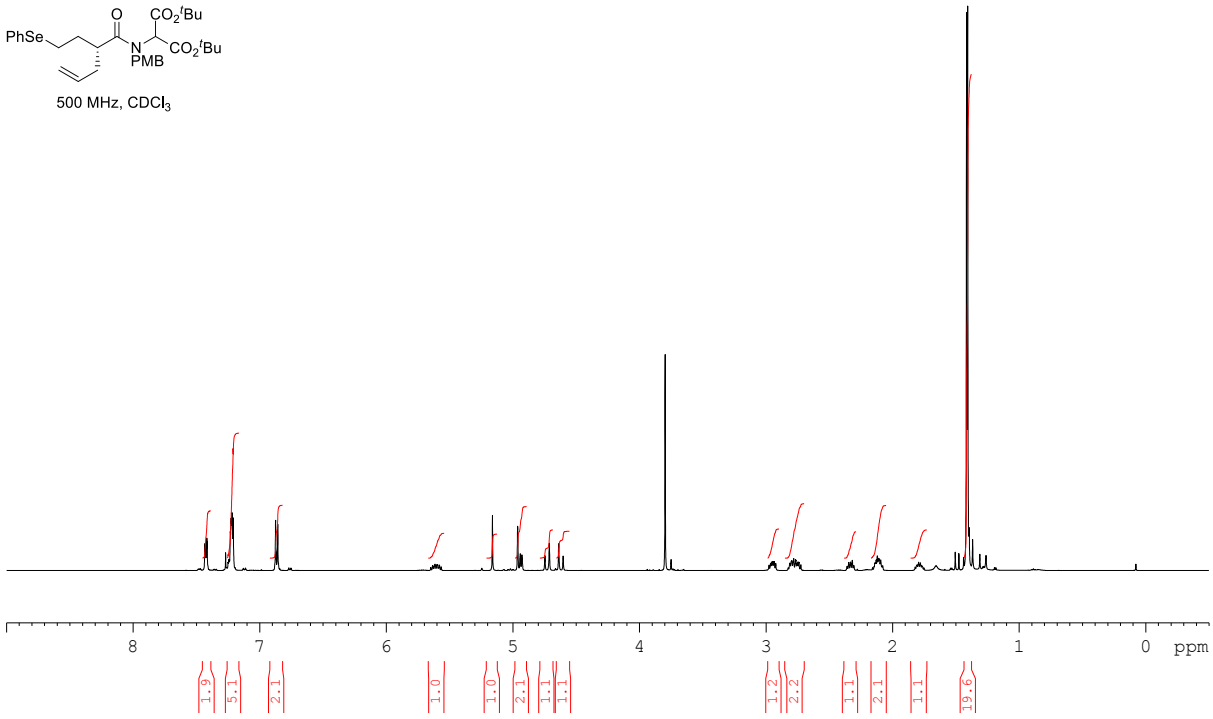


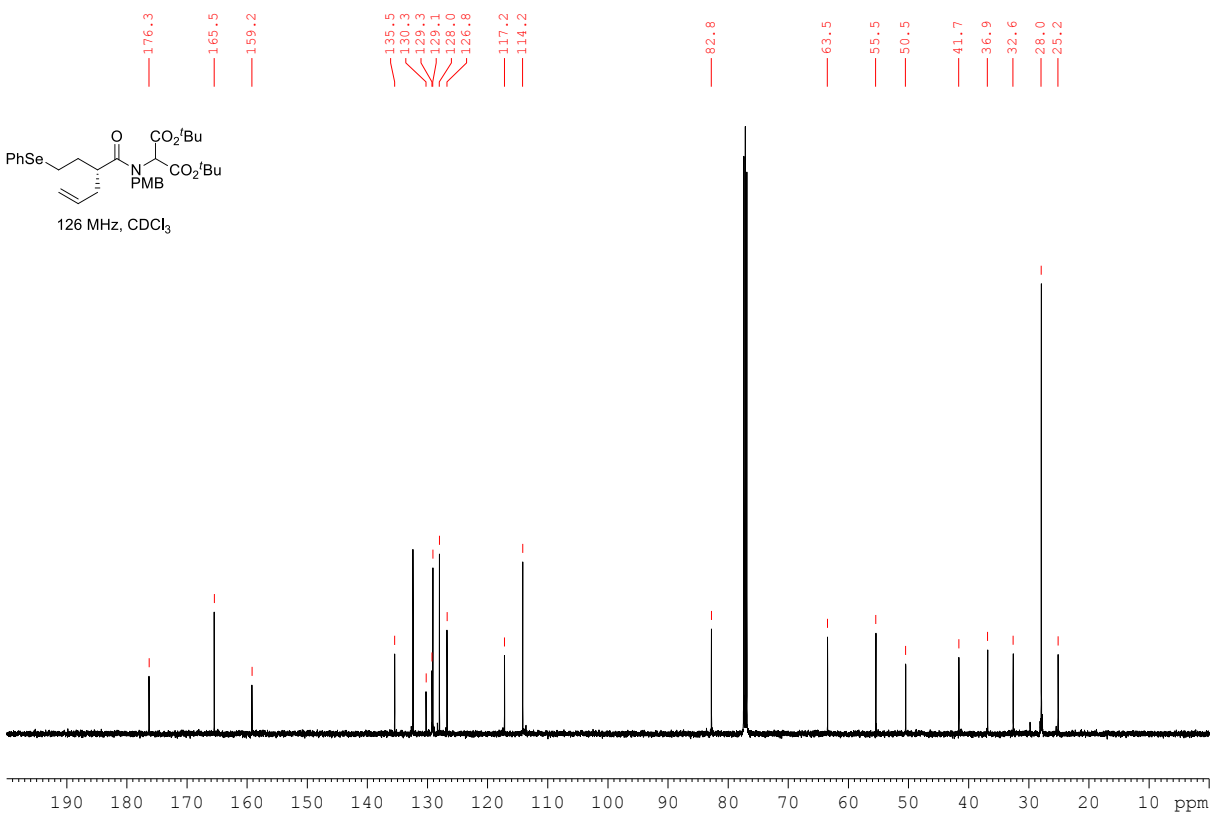
Spectra for compound **S22**



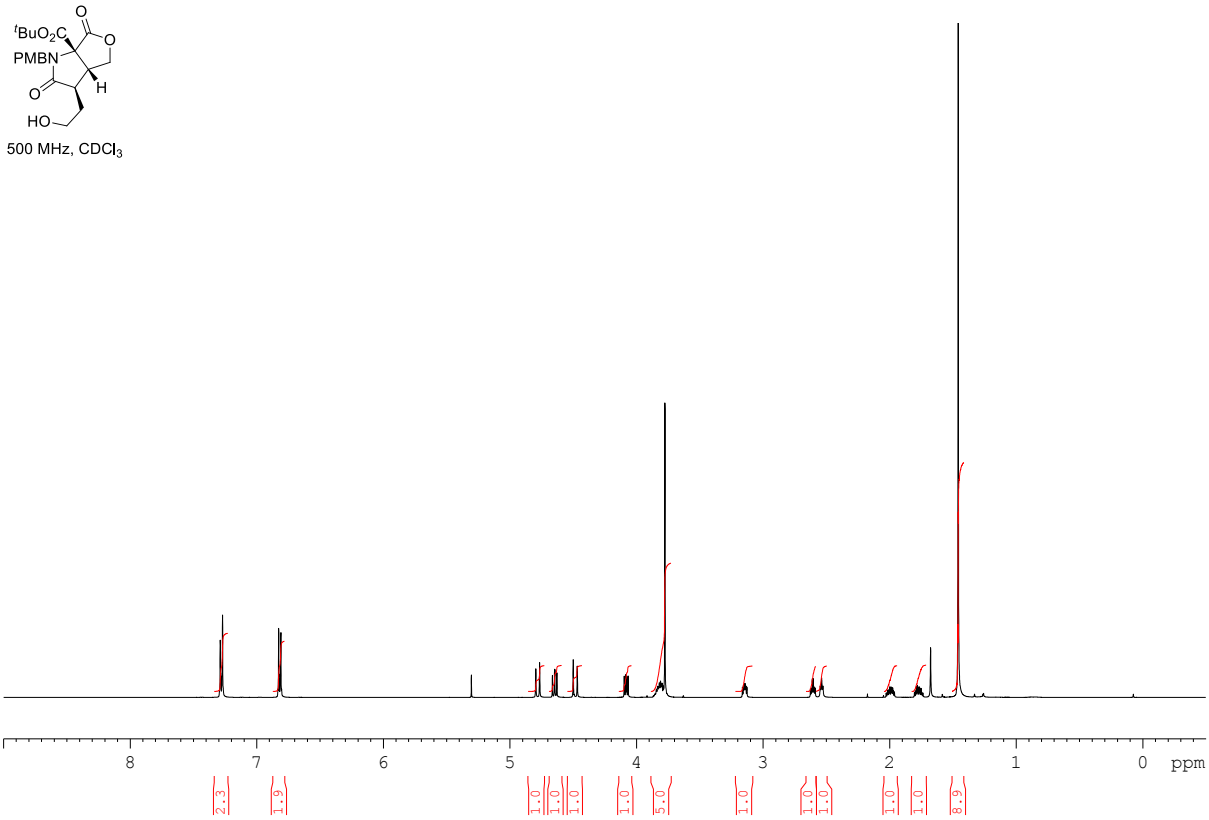


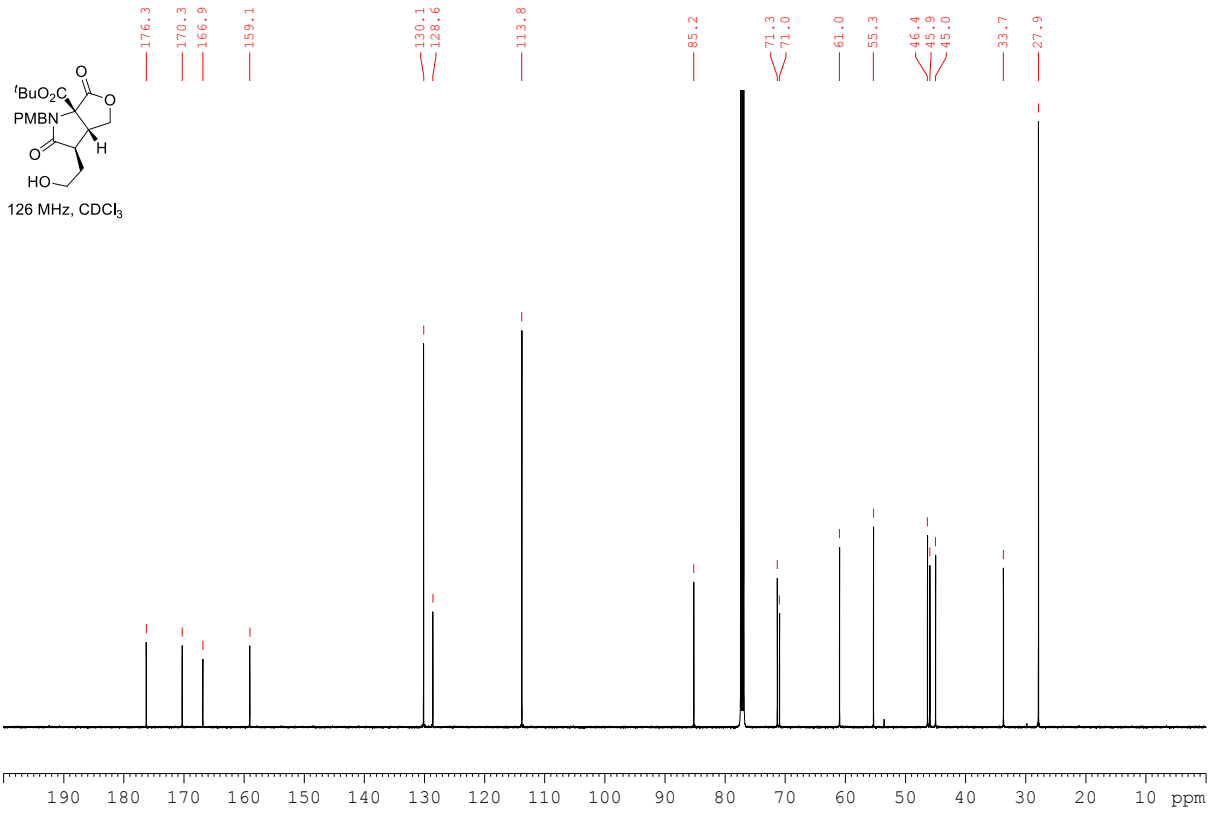
Spectra for compound **23**



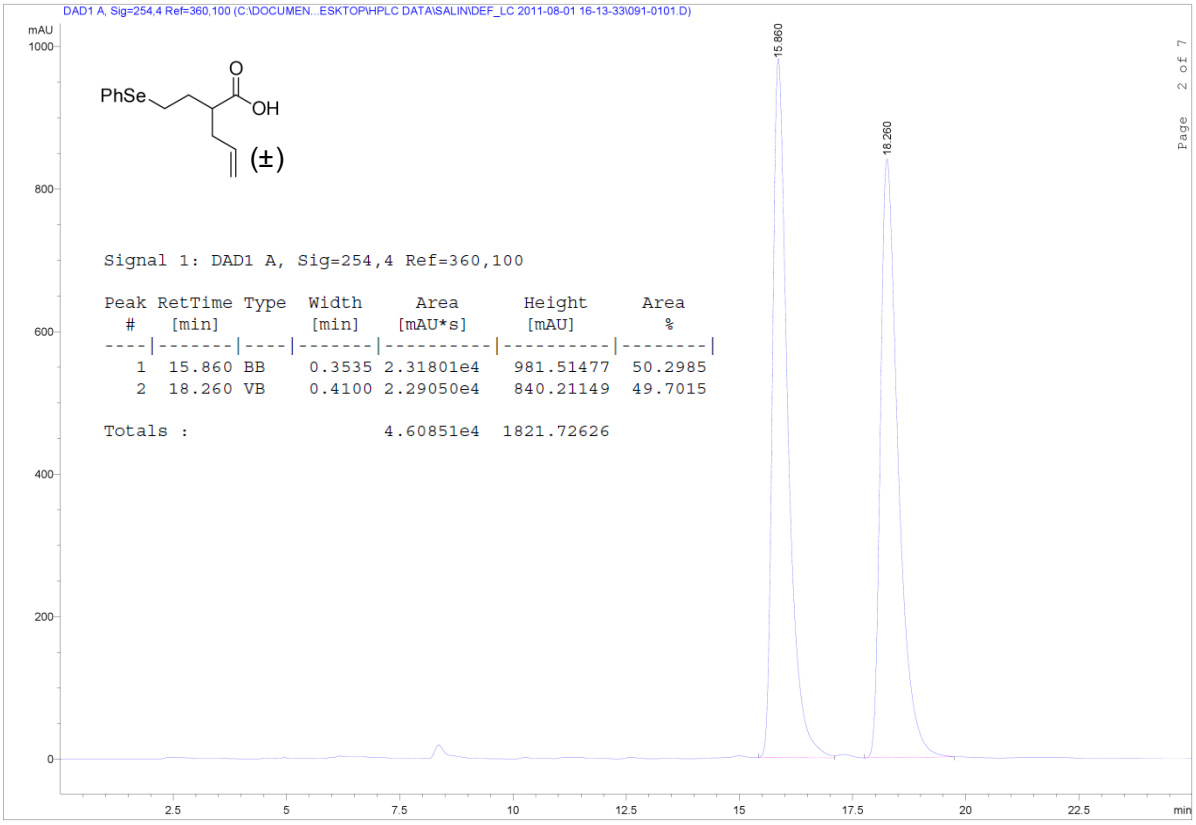


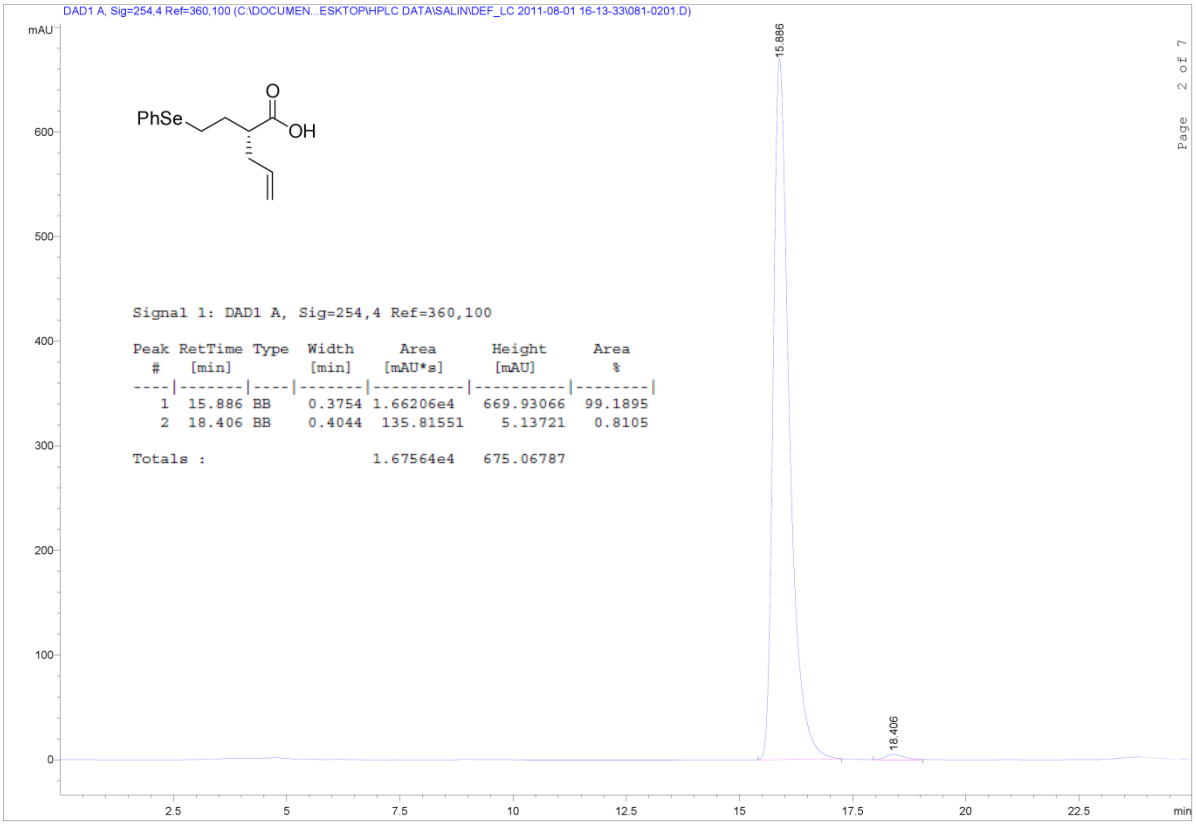
Spectra for compound **24**





HPLC traces for compound **S22** (ChiralPak AD-H, 5% IPA in hexane, 0.700 mL/min)





HPLC traces for compound **24**(ChiralPak AD-H, 10% IPA in hexane, 1.00 mL/min)