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Palladium-Catalysed Cyclisation of *N*-Alkynyl Aminomalonates

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Palladium-catalyzed cyclization of *N*-alkynyl amino malonates

Wilfried Hess and Jonathan W. Burton*

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Introduction

¹H and ¹³C NMR spectra were recorded on Bruker DPX-400, DRX-400, AVC-500 or AVB-500 using deutero chloroform as an internal deuterium lock. Chemical shifts are quoted in units of δ relative to tetramethylsilane ($\delta=0$). Multiplets are indicated as s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; dd, double doublet; m, multiplet; br, broad, etc. Coupling constants J are quoted in Hz. ¹³C spectra were recorded with proton decoupling; HMQC, were recorded to assist assignment.

Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. The samples were prepared as a thin film and the intensity of the peak is indicated with w, weak, m, medium, and s, strong.

Mass spectra were recorded by the Mass Spectrometry Service at the Chemical Research Laboratory, University of Oxford.

Flash chromatography was carried out on silica gel [Merck 9385 Kieselgel 60 (230-400 ASTM)]. Analytical TLC was carried out on 0.25 mm thick plates precoated with Merck Kieselgel F₂₅₄ silica gel and visualised by UV and aqueous potassium permanganate solution, ethanolic phosphomolybdic acid solution or ninhydrin in ethanol.

Semi-preparative HPLC was performed on an Agilent 1200 series LC using a Zorbax RX-silica column (9.4 × 250 mm, 5 μ m).

Kugelrohr bulb-to-bulb distillations were carried out using a Büchi GKR-51 machine. Boiling points are oven temperatures.

Solvents were purified by standard techniques. Ether refers to diethyl ether. Petroleum ether (PE) refers to the fraction boiling at 40-60 °C. But-3-ynyl 4-methylbenzenesulfonate was synthesised according to the procedure of *Walther*.^[1]

4-Phenylbut-3-yn-1-ol was synthesised by the procedure of *Zhang*.^[2]

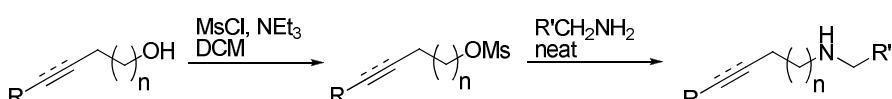
Di-*tert*-butyl 2-bromomalonate was synthesised according to the procedure of *Spino*.^[3]

tert-Butyldimethyl(3-iodobut-3-enyloxy)silane was synthesised according to the procedure of *Narender* followed by a standard silylation procedure.^[4]

(iodoethynyl)benzene was synthesised according to the procedure of *Xue*.^[5] The α -amino malonates were prepared according to the method of *Chai*.^[6]

1. Synthesis of the cyclization precursors

1. 1. Synthesis of benzyl-, methyl-, or PMB-protected amines

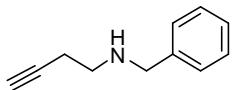


General procedure 1 for the alkylation of benzylamines with alkynyl mesylates:

1.0 eq. alcohol was dissolved in DCM and 1.5 eq. NEt₃ was added. The reaction mixture was cooled to 0 °C (ice bath), 1.0 eq. mesyl chloride was added dropwise and the reaction was stirred for 2 h at room temperature. Then water was added and the organic layer separated. The organic layer was washed with 1 M HCl, sat. NaHCO₃ sol., brine and dried (MgSO₄). After evaporation of the solvent the crude mesylate was used in the next step without further purification.

The mesylate was added dropwise to neat benzylamine and the reaction was stirred at room temperature overnight. Then 2 M NaOH and Et₂O were added. The organic layer was separated and the aqueous layer was extracted 2× with Et₂O. The combined organic layers were dried (MgSO₄) and the solvent was removed. The crude product was then purified by FC.

N-Benzylbut-3-yn-1-amine

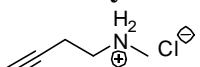


But-3-ynyl methanesulfonate (7.41 g, 50 mmol, 1.0 eq.) was added dropwise to benzyl amine (32.77 mL, 300 mmol, 6.0 eq.) and the mixture stirred for 15 h at RT. Then, 1 M NaOH (400 mL) and Et₂O (200 mL) were added and the organic layer was separated. The aqueous layer was extracted 2× with Et₂O, the combined organic layers dried (MgSO₄) and the solvent evaporated. Purification by FC (EtOAc, R_f (EtOAc) = 0.35) afforded *N*-benzylbut-3-yn-1-amine (6.54 g, 41 mmol, 82%) as a clear and colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.33 (d, 4H, J = 4.4 Hz, H_{ar}), 7.28-7.23 (m, 1H, H_{ar}), 3.82 (s, 2H, CH₂Ph), 2.81 (t, 2H, J = 6.6 Hz, CH₂N), 2.42 (td, 2H, J = 6.6, 2.6 Hz, CH₂CC), 2.00 (t, 1H, J = 2.6 Hz, CCH), 1.61 (bs, 1H, NH). ¹³C-NMR (100 MHz, CDCl₃): 140.1 (C_{ar}), 128.4 (2×CH_{ar}), 128.1 (2×CH_{ar}), 127.0 (CH_{ar}), 82.5 (C_{sp}), 69.5 (CH_{sp}), 53.3 (CH₂Ph), 47.3 (CH₂N), 19.5 (CH₂C). MS (ESI+): 160 (100, [M+H]⁺), 317 (20, [2M-H]⁺).

The analytical data is in accordance with the literature.^[7]

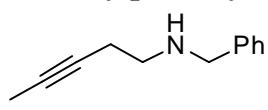
N-Methylbut-3-yn-1-amine hydrochloride



But-3-ynyl methanesulfonate (7.41 g, 50 mmol, 1.0 eq.) was added dropwise to a solution of methylamine in EtOH (28 mL, 33 wt. %, 224 mmol, 4.5 eq.) and the mixture stirred for 5 d at RT followed by distillation (1 atm, 80-160 °C). Afterwards the distillate and the remaining residue were combined, made basic with 1 M NaOH and extracted 3× with EtOAc. The combined organic layers were then extracted with 1 M HCl (4× 50 mL). The combined aqueous layers were made basic with 2 N NaOH (200 mL) and extracted again with EtOAc (4× 50 mL). The combined organic layers were dried (MgSO₄) and HCl in Et₂O (50 mL, 1.1 M, 55 mmol, 1.1 eq.) was added (a small second layer was separated). The mixture was freed from all volatiles, the residue dissolved in isopropanol, dried again (MgSO₄) and the solvent evaporated. After drying under vacuum the residue solidified to give *N*-methylbut-3-yn-1-amine hydrochloride (3.31 g with 10 mol% isopropanol, 14.7 mmol, 29%) as a semi-solid. The product was used without further purification.

¹H-NMR (400 MHz, D₂O): 3.10 (t, 2H, J = 6.4 Hz, CH₂N), 2.63 (s, 3H, CH₃), 2.54 (td, 2H, J = 6.5, 2.7 Hz, CH₂CC), 2.38 (td, 1H, J = 2.7, 0.8 Hz, CCH).

N-Benzylpent-3-yn-1-amine



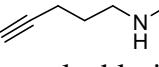
According to GP1 the mesylate was prepared from pent-3-yn-1-ol (2.31 g, 25 mmol, 1.0 eq.), NEt₃ (5.22 mL, 37.5 mmol, 1.5 eq.) and mesyl chloride (1.94 mL, 25 mmol, 1.0 eq.) in DCM (50 mL). This was then converted into the title compound with benzyl amine (16.38 mL, 150 mmol, 6.0 eq.) and after FC (EtOAc, R_f (EtOAc) = 0.26) *N*-benzylpent-3-yn-1-amine (2.98 g, 17.2 mmol, 69%) was obtained as a colorless oil.

Mesylate: ¹H-NMR (400 MHz, CDCl₃): 4.27 (t, 2H, J = 6.9 Hz, CH₂O), 3.05 (s, 3H, SO₂CH₃), 2.60 (tq, 2H, J = 6.9, 2.5 Hz, CH₂CC), 1.79 (t, 3H, J = 2.5 Hz, CCCH₃).

Amine: $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.38-7.31 (*m*, 4H, H_{ar}), 7.28-7.24 (*m*, 1H, H_{ar}), 3.83 (*s*, 2H, CH_2Ph), 2.76 (*t*, 2H, $J = 6.6$ Hz, CH_2N), 2.37 (*tq*, 2H, $J = 6.5, 2.6$ Hz, CH_2CC), 1.79 (*t*, 3H, $J = 2.6$ Hz, CH_3), 1.73 (*bs*, 1H, NH).

The $^1\text{H-NMR}$ data is in accordance with the literature.^[8]

N-Benzylpent-4-yn-1-amine

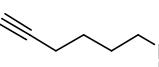
 According to GP1 the mesylate was prepared from pent-4-yn-1-ol (2.79 g, 30 mmol, 1.0 eq.), NEt_3 (6.27 mL, 45 mmol, 1.5 eq.) and mesyl chloride (2.32 mL, 30 mmol, 1.0 eq.) in DCM (100 mL). This was then converted into the title compound with benzyl amine (19.66 mL, 180 mmol, 6.0 eq.). Purification by FC (EtOAc) afforded *N*-benzylpent-4-yn-1-amine (4.15 g, 24.0 mmol, 80%) as a colorless oil.

Mesylate: $^1\text{H-NMR}$ (400 MHz, CDCl_3): 4.36 (*t*, 2H, $J = 6.1$ Hz, CH_2O), 3.03 (*s*, 3H, CH_3), 2.37 (*dt*, 2H, $J = 6.8, 2.7$ Hz, CH_2CC), 2.01 (*t*, 1H, $J = 2.7$ Hz, CCH), 2.00-1.94 (*m*, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$).

Amine: $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.35-7.31 (*m*, 4H, H_{ar}), 7.29-7.23 (*m*, 1H, H_{ar}), 3.80 (*s*, 2H, CH_2Ph), 2.76 (*t*, 2H, $J = 7.0$ Hz, CH_2N), 2.28 (*td*, 2H, $J = 7.0, 2.7$ Hz, CH_2CC), 1.96 (*t*, 1H, $J = 2.7$ Hz, CCH), 1.74 (*qn*, 2H, $J = 7.1$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.50 (*bs*, 1H, NH).

The $^1\text{H-NMR}$ data is in accordance with the literature.^[9]

N-Benzylhex-5-yn-1-amine

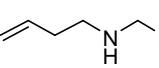
 According to GP1 the mesylate was prepared from 5-hexynol (3.31 mL, 30 mmol, 1.0 eq.), NEt_3 (6.27 mL, 45 mmol, 1.5 eq.) and mesyl chloride (2.32 mL, 30 mmol, 1.0 eq.) in DCM (100 mL). This was then converted into the title compound with benzyl amine (19.66 mL, 180 mmol, 6.0 eq.). Purification by FC (EtOAc) afforded the desired product (5.04 g, 26.9 mmol, 90%) as a yellow oil.

Mesylate: $^1\text{H-NMR}$ (400 MHz, CDCl_3): 4.27 (*t*, 2H, $J = 6.3$ Hz, CH_2O), 3.02 (*s*, 3H, CH_3), 2.27 (*td*, 2H, $J = 6.9, 2.6$ Hz, CH_2CC), 1.98 (*t*, 1H, $J = 2.6$ Hz, CCH), 1.93-1.86 (*m*, 2H, $\text{CH}_2\text{CH}_2\text{O}$), 1.70-1.63 (*m*, 2H, $\text{CH}_2\text{CH}_2\text{CC}$).

Amine: $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.37-7.23 (*m*, 5H, H_{ar}), 3.80 (*s*, 2H, CH_2Ph), 2.66 (*t*, 2H, $J = 6.9$ Hz, CH_2N), 2.21 (*td*, 2H, $J = 6.8, 2.6$ Hz, CH_2CC), 1.95 (*t*, 1H, $J = 2.7$ Hz, CH_2), 1.68-1.50 (*m*, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$).

The $^1\text{H-NMR}$ data is in accordance with the literature.^[10]

N-Benzylbut-3-en-1-amine

 According to GP1 the mesylate was prepared from but-3-en-1-ol (3.44 mL, 40 mmol, 1.0 eq.), NEt_3 (8.36 mL, 60 mmol, 1.5 eq.) and mesyl chloride (3.01 mL, 40 mmol, 1.0 eq.) in DCM (100 mL). This was then converted into the title compound with benzyl amine (26.22 mL, 240 mmol, 6.0 eq.). Purification by FC (EtOAc) afforded *N*-benzylbut-3-en-1-amine (5.32 g, 33.0 mmol, 83%) as a colorless oil.

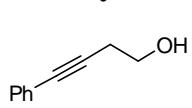
Mesylate: $^1\text{H-NMR}$ (200 MHz, CDCl_3): 5.80 (*ddt*, 1H, $J = 16.9, 10.2, 6.7$ Hz, H_{olef}), 5.24-5.13 (*m*, 2H, H_{olef}), 4.28 (*t*, 2H, $J = 6.7$ Hz, CH_2O), 3.02 (*s*, 3H, CH_3), 2.52 (*tq*, 2H, $J = 6.7, 1.3$ Hz, $\text{CH}_2\text{C}=\text{C}$).

The $^1\text{H-NMR}$ data is in accordance with the literature.^[11]

Amine: $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.36-7.31 (*m*, 4H, H_{ar}), 7.29-7.24 (*m*, 1H, H_{ar}), 5.80 (*ddt*, 1H, $J = 17.1, 10.2, 6.8$ Hz, H_{olef}), 5.10 (*ddd*, 1H, $J = 17.1, 3.4, 1.5$ Hz, H_{olef}), 5.05 (*tdd*, 1H, $J = 10.2, 2.0, 1.5$ Hz, H_{olef}), 3.81 (*s*, 2H, CH_2Ph), 2.72 (*t*, 2H, $J = 6.8$ Hz, CH_2N), 2.30 (*tq*, 2H, $J = 6.8, 1.2$ Hz, $\text{CH}_2\text{C}=\text{C}$), 1.58 (*bs*, 1H, NH).

The ^1H -NMR data is in accordance with the literature.^[12]

4-Phenylbut-3-yn-1-ol

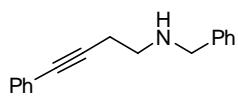


To dry NEt_3 (100 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (351 mg, 0.5 mmol, 2.0 mol%), CuI (48 mg, 0.25 mmol, 1.0 mol%), phenyl iodide (2.80 mL, 25.0 mmol, 1.0 eq.) and 3-butyn-1-ol (2.27 mL, 30 mmol, 1.2 eq.). The reaction was heated to 60 °C for 2 h. A white precipitate appeared and the reaction became green-brown. After cooling the reaction mixture was diluted by addition of Et_2O and filtered through a plug of silica (eluent: Et_2O). Then the solvent was removed. Purification by FC (PE/ Et_2O 1:2) afforded 4-phenylbut-3-yn-1-ol (3.42 g, 23.4 mmol, 93%) as a brown oil.

^1H -NMR (400 MHz, CDCl_3): 7.43-7.40 (*m*, 2H, H_{ar}), 7.31-7.28 (*m*, 3H, H_{ar}), 3.82 (*t*, 2H, *J* = 6.3 Hz, CH_2O), 2.70 (*t*, 2H, *J* = 6.3 Hz, CH_2CC), 1.83 (*bs*, 1H, OH).

The ^1H -NMR data is in accordance with the literature.^[2]

N-Benzyl-4-phenylbut-3-yn-1-amine



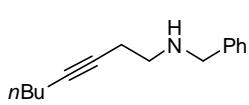
According to GP1 the mesylate was prepared from 4-phenylbut-3-yn-1-ol (3.41 g, 23.4 mmol, 1.0 eq.), NEt_3 (4.90 mL, 35.1 mmol, 1.5 eq.) and mesyl chloride (1.81 mL, 23.4 mmol, 1.0 eq.) in DCM (50 mL). This was then converted into the title compound with benzyl amine (17.04 mL, 140.4 mmol, 6.0 eq.). Purification by FC (pure Et_2O) afforded *N*-benzyl-4-phenylbut-3-yn-1-amine (3.73 g, 15.9 mmol, 68%) as a colorless oil.

Mesylate: ^1H -NMR (200 MHz, CDCl_3): 7.42-7.39 (*m*, 2H, H_{ar}), 7.33-7.29 (*m*, 3H, H_{ar}), 4.40 (*t*, 2H, *J* = 6.8 Hz, CH_2O), 3.08 (*s*, 3H, CH_3), 2.90 (*t*, 2H, *J* = 6.8 Hz, CH_2CC).

Amine: ^1H -NMR (400 MHz, CDCl_3): 7.42-7.25 (*m*, 10H, H_{ar}), 3.88 (*s*, 2H, CH_2Ph), 2.90 (*t*, 2H, *J* = 6.6 Hz, CH_2N), 2.66 (*t*, 2H, *J* = 6.6 Hz, CH_2CC), 1.80 (*s*, 1H, NH).

^{13}C -NMR (100 MHz, CDCl_3): 140.3 (C_{ar}), 131.7 (2 \times CH_{ar}), 128.5 (2 \times CH_{ar}), 128.3 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 127.8 (CH_{ar}), 127.0 (CH_{ar}), 123.7 (C_{ar}), 88.0 (C), 81.9 (C), 53.5 (CH_2), 47.7 (CH_2), 20.6 (CH_2). IR (film): 3306w, 3081w, 3060w, 3027w, 2910m, 2833m, 1598w, 1490m, 1453m, 1442m, 1119m, 1070w, 1027w, 755s, 736m, 692s. MS (ESI+): 236.14 (100, $[\text{M}+\text{H}]^+$). HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{18}\text{N}$ ($[\text{M}+\text{H}]^+$) 236.1434, found 236.1432.

N-Benzyloct-3-yn-1-amine



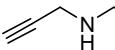
According to GP1 the mesylate was prepared from oct-3-yn-1-ol (5.22 g, 41.4 mmol, 1.0 eq.), NEt_3 (8.65 mL, 62.1 mmol, 1.5 eq.) and mesyl chloride (3.20 mL, 41.4 mmol, 1.0 eq.) in DCM (100 mL). This was then converted into the title compound with benzyl amine (27.14 mL, 248.4 mmol, 6.0 eq.). Purification by FC (EtOAc) afforded *N*-benzyloct-3-yn-1-amine (7.81 g, 36.3 mmol, 88%) as a colorless oil.

Mesylate: ^1H -NMR (200 MHz, CDCl_3): 4.27 (*t*, 2H, *J* = 6.9 Hz, CH_2O), 3.05 (*s*, 3H, SO_2CH_3), 2.62 (*tt*, 2H, *J* = 6.9, 2.3 Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.15 (*tt*, 2H, *J* = 7.0, 2.3 Hz, CH_2CC), 1.50-1.34 (*m*, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 0.90 (*t*, 3H, *J* = 7.1 Hz, CH_2CH_3).

Amine: ^1H -NMR (400 MHz, CDCl_3): 7.35-7.31 (*m*, 4H, H_{ar}), 7.29-7.24 (*m*, 1H, H_{ar}), 3.83 (*s*, 2H, CH_2Ph), 2.76 (*t*, 2H, *J* = 6.5 Hz, CH_2N), 2.40 (*tt*, 2H, *J* = 6.5, 2.4 Hz, $n\text{PrCH}_2$), 2.16 (*tt*, 2H, *J* = 7.9, 2.3 Hz, $\text{CH}_2\text{CH}_2\text{N}$), 1.76 (*bs*, 1H, NH), 1.50-1.35 (*m*, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.90 (*t*, 3H, *J* = 7.2 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3): 140.3 (C_{ar}), 128.4 (2 \times CH_{ar}), 128.1 (2 \times CH_{ar}), 126.9 (CH_{ar}), 81.7 (C), 77.8 (C), 53.4 (CH_2), 47.9 (CH_2), 31.1 (CH_2), 22.0 (CH_2), 19.8 (CH_2), 18.4 (CH_2), 13.6 (CH_3). IR (film):

3313w, 3085w, 3062w, 3027w, 2956s, 2930s, 2871m, 2860m, 2840m, 1494w, 1454s, 1330w, 1119m, 735s, 698s. MS (ESI+): 216.18 (100, $[M+H]^+$). HRMS (ESI): calculated for $C_{15}H_{22}N$ ($[M+H]^+$) 216.1747, found 216.1744.

N-Benzylprop-2-yn-1-amine

 To benzylamine (19.66 mL, 180 mmol, 6.0 eq.) was added dropwise propargyl bromide (3.34 mL, 80 wt. % in toluene, 30 mmol, 1.0 eq.).

The reaction was stirred for 15 h at room temperature and then 2 M NaOH and Et₂O were added. The organic layer was separated and the aqueous layer was extracted 2× with Et₂O. The combined organic layers were dried (MgSO₄) and the solvent removed. After purification by FC (EtOAc) *N*-benzylprop-2-yn-1-amine (3.36 g, 23.1 mmol, 77%) was obtained as a clear oil.

¹H-NMR (400 MHz, CDCl₃): 7.38-7.31 (*m*, 4H, H_{ar}), 7.29-7.25 (*m*, 1H, H_{ar}), 3.90 (*s*, 2H, CH₂Ph), 3.44 (*d*, 2H, *J* = 2.4 Hz, CH₂CC), 2.27 (*t*, 1H, *J* = 2.4 Hz, CCH), 1.51 (*s*, 1H, NH).

The ¹H-NMR data is in accordance with the literature.^[13]

N-(4-Methoxybenzyl)but-3-yn-1-amine

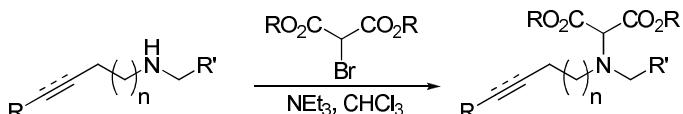
 To but-3-yn-1-ol (2.27 g, 30 mmol, 1.0 eq.) dissolved in DCM (100 mL) was added dropwise NEt₃ (6.27 mL, 45 mmol, 1.5 eq.). The mixture was cooled to 0 °C (ice bath) and mesyl chloride (2.32 mL, 30 mmol, 1.0 eq.) was added dropwise. After complete addition the reaction was stirred at room temperature for 2 h and then water (100 mL) was added and the organic layer was separated. It was then washed with 1 M HCl, sat. NaHCO₃ sol. and brine. After drying (MgSO₄) and evaporation of the solvent the mesylate was obtained as a slightly yellow oil which was used without further purification.

The mesylate was dissolved in CHCl₃ (100 mL) and 4-methoxy benzyl amine (6.15 mL, 47.1 mmol, 2.0 eq.) and NEt₃ (6.56 mL, 47.1 mmol, 2.0 eq.) were added. The reaction was stirred for 2 d at 80 °C after which TLC indicated approximately 80% conversion. Then 1 M NaOH was added and the organic layer was separated and the aqueous layer was extracted 2× with DCM. The combined organic layers were dried (MgSO₄) and the solvent was removed. Purification by FC (Et₂O) afforded *N*-(4-methoxybenzyl)but-3-yn-1-amine (2.27 g, 12.0 mmol, 51%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.26-7.23 (*m*, 2H, H_{ar}), 6.89-6.86 (*m*, 2H, H_{ar}), 3.81 (*s*, 3H, OCH₃), 3.76 (*s*, 2H, CH₂Ar), 2.80 (*t*, 2H, *J* = 6.6 Hz, CH₂N), 2.42 (*td*, 1H, *J* = 6.6, 2.6 Hz, CH₂CC), 2.00 (*t*, 1H, *J* = 2.6 Hz, CCH), 1.63 (bs, 1H, NH).

The ¹H-NMR data is in accordance with the literature.^[14]

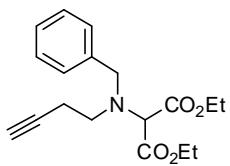
1. 2. Synthesis of the N-alkyl alkynyl and alkenyl amino malonates



General procedure 2 for the alkylation of amines with 2-bromo malonates: The amine, NEt₃ and the 2-bromomalonate were dissolved in CHCl₃ and heated to 80 °C for 15 h - 3 d. The reaction was monitored by TLC. After complete conversion 1 M NaOH was added and the organic layer was separated. The aqueous layer was extracted 2-3× with EtOAc or Et₂O. The combined organic layers were washed with

water, brine, dried (MgSO_4) and the solvent was evaporated. The crude product was then purified by FC.

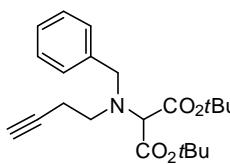
Diethyl 2-(benzyl(but-3-ynyl)amino)malonate 4



According to GP2 *N*-benzylbut-3-yn-1-amine (9.25 g, 58.0 mmol, 1.5 eq.), diethyl 2-bromomalonate (92% pure, 7.15 mL, 38.6 mmol, 1.0 eq.) and NEt_3 (10.77 mL, 77.3 mmol, 2.0 eq.) were heated at reflux in CHCl_3 (100 mL) for 3 d. Purification by FC (DCM, R_f (DCM/PE 4:1) = 0.42) afforded diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (7.53 g, 23.7 mmol, 61%) as a yellow oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.40-7.38 (*m*, 2H, H_{ar}), 7.33-7.29 (*m*, 2H, H_{ar}), 7.27-7.25 (*m*, 1H, H_{ar}), 4.23 (*q*, 4H, *J* = 7.2 Hz, CH_2), 4.20 (*s*, 1H, $\text{CH}(\text{CO})_2$), 3.94 (*s*, 2H, CH_2Ph), 2.99 (*t*, 2H, *J* = 7.4 Hz, CH_2N), 2.36 (*td*, 2H, *J* = 7.4, 2.7 Hz, CH_2CC), 1.94 (*t*, 1H, *J* = 2.7 Hz, CCH), 1.29 (*t*, 6H, *J* = 7.1 Hz, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 168.1 (2 \times CO), 138.8 (C_{ar}), 128.5 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 127.2 (CH_{ar}), 82.4 (C_{sp}), 69.1 ($\text{CH}_{\text{sp}3}$), 66.8 (CH_{sp}), 61.2 (2 \times CH_2), 56.2 (CH_2), 50.2 (CH_2), 19.0 (CH_2), 14.1 (2 \times CH_3). IR (film): 3291m, 2982m, 2937w, 2852w, 1733s, 1494w, 1453w, 1370w, 1301m, 1231m, 1149s, 1029m, 741w, 699w, 638w. MS (ESI+): 318.2 (100, $[\text{M}+\text{H}]^+$). HRMS (ESI): calculated for $\text{C}_{18}\text{H}_{23}\text{NNaO}_4$ ($[\text{M}+\text{Na}]^+$) 340.1519, found 340.1516.

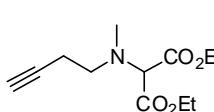
Di-*tert*-butyl 2-(benzyl(but-3-ynyl)amino)malonate 7a



According to GP2 *N*-benzyl butynylamine (3.13 g, 19.6 mmol, 1.0 eq.), di-*tert*-butyl 2-bromomalonate (6.45 g, 21.9 mmol, 1.1 eq.) and NEt_3 (5.46 mL, 39.2 mmol, 2.0 eq.) were heated at reflux in CHCl_3 (100 mL) for 15 h. Purification by FC (DCM/PE 3:1) afforded of a mixture of product and starting material (4.50 g, 1.0:1.1). This mixture was reacted under identical conditions with *N*-benzyl butynylamine (2.25 g, 14.16 mmol, 2.0 eq.), NEt_3 (1.97 mL, 14.16 mmol, 2.0 eq.) in CHCl_3 (50 mL) for 3 d. After work up and FC (DCM) the product was obtained as a mixture with the bromomalonate (4.07 g, 4:1). The bromomalonate was distilled off by Kugelrohr distillation (7 mbar, 200 °C) which gave after further FC (DCM) di-*tert*-butyl 2-(benzyl(but-3-ynyl)amino)malonate **7a** (2.75 g, 7.4 mmol, 38%) as yellow oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.42-7.40 (*m*, 2H, H_{ar}), 7.33-7.30 (*m*, 2H, H_{ar}), 7.27-7.25 (*m*, 1H, H_{ar}), 4.00 (*s*, 1H, $\text{CH}(\text{CO})_2$), 3.94 (*s*, 2H, CH_2Ph), 2.99 (*t*, 2H, *J* = 7.5 Hz, CH_2N), 2.36 (*td*, 2H, *J* = 7.5, 2.6 Hz, CH_2CC), 1.94 (*t*, 1H, *J* = 2.6 Hz, CCH), 1.49 (*s*, 18H, *tBu*). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 167.5 (CO), 139.3 (C_{ar}), 128.6 (2 \times CH_{ar}), 128.3 (2 \times CH_{ar}), 127.1 (CH_{ar}), 82.6 (2 \times $\text{C}_{\text{sp}3}$), 82.0 (C_{sp}), 69.1 ($\text{CH}_{\text{sp}3}$), 68.4 (CH_{sp}), 56.2 (CH_2), 51.1 (CH_2), 28.0 (6 \times CH_3), 19.1 (CH_2). IR (film): 3060w, 3025w, 2976m, 2931w, 2832w, 1725s, 1494w, 1454w, 1392w, 1368m, 1275m, 1255m, 1147s, 1024w, 983w, 841w, 736w, 696m. MS (ESI+): 374.3 (100, $[\text{M}+\text{H}]^+$). HRMS (ESI): calculated for $\text{C}_{22}\text{H}_{31}\text{NNaO}_4$ ($[\text{M}+\text{Na}]^+$) 396.2145, found 396.2150.

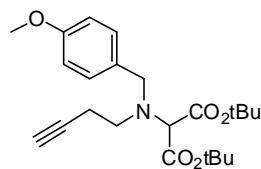
Diethyl 2-(but-3-ynyl(methyl)amino)malonate 7b



According to GP2 *N*-methyl butynylamine hydrochloride (2.50 g, 23.7 mmol, 1.5 eq.), diethyl 2-bromomalonate (92% pure, 2.68 mL, 15.8 mmol, 1.0 eq.) and NEt_3 (9.89 mL, 71.0 mmol, 4.5 eq.) were heated at reflux in CHCl_3 (100 mL) for 3 d. Purification by FC (PE/EtOAc 1:1) afforded diethyl 2-(but-3-ynyl(methyl)amino)malonate **7b** (2.39 g, 9.9 mmol, 63%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 4.25 (*q*, 4H, *J* = 7.2 Hz, 2×OCH₂), 4.15 (*s*, 1H, CH), 2.89 (*t*, 2H, *J* = 7.5 Hz, CH₂N), 2.52 (*s*, 3H, NCH₃), 2.40 (*dt*, 2H, *J* = 7.5, 2.7 Hz, CH₂CC), 1.97 (*t*, 1H, *J* = 2.7 Hz, CCH), 1.30 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 167.5 (2×CO), 82.3 (C_{sp}), 70.2 (CH_{sp}), 69.1 (CH_{sp3}), 61.3 (2×CH₂), 53.5 (CH₃), 39.6 (CH₂), 18.3 (CH₂), 14.1 (2×CH₃). IR (film): 3288m, 2983m, 2940w, 2906w, 1733s, 1465w, 1370w, 1301m, 1235m, 1176m, 1153m, 1095w, 1069m, 1028m, 639w. MS (ESI+): 242.2 (100, [M+H]⁺). HRMS (ESI): calculated for C₁₂H₁₉NaNO₄ ([M+Na]⁺) 264.1206 found 264.1210.

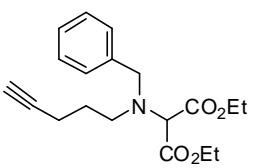
Di-*tert*-butyl 2-(but-3-ynyl(4-methoxybenzyl)amino)malonate 7c



According to GP2 *N*-(4-methoxybenzyl)but-3-yn-1-amine (2.58 g, 13.6 mmol, 1.5 eq.), di-*tert*-butyl 2-bromomalonate (2.69 g, 9.1 mmol, 1.0 eq.) and NEt₃ (2.53 mL, 18.2 mmol, 2.0 eq.) were heated at reflux in CHCl₃ (100 mL) for 3 d. Purification by FC (PE/DCM 2:3 then Et₂O, R_f (DCM/PE 3:1) = 0.18) afforded di-*tert*-butyl 2-(but-3-ynyl(4-methoxybenzyl)amino)malonate 7c (2.49 g, 6.2 mmol, 68%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.31 (*d*, 2H, *J* = 8.4 Hz, H_{ar}), 6.84 (*d*, 2H, *J* = 8.4 Hz, H_{ar}), 3.97 (*s*, 1H, CH), 3.85 (*s*, 2H, CH₂Ar), 3.79 (*s*, 3H, OCH₃), 2.96 (*t*, 2H, *J* = 7.5 Hz, CH₂N), 2.35 (*td*, 2H, *J* = 7.8, 2.5 Hz, CH₂CC), 1.93 (*t*, 1H, *J* = 2.3 Hz, CCH), 1.48 (*s*, 18H, 2×C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃): 167.5 (2×CO), 158.8 (C_{ar}), 131.1 (C_{ar}), 129.8 (2×CH_{ar}), 113.6 (2×CH_{ar}), 82.7 (C_{sp}), 82.0 (2×C), 69.1 (CH_{sp}), 68.2 (C), 55.59 (CH₃), 55.2 (CH₂), 50.9 (CH₂), 28.0 (6×CH₃), 19.1 (CH₂). IR (film): 3289m, 2978m, 2934w, 2837w, 1727s, 1612w, 1512m, 1457w, 1368m, 1247s, 1141s, 1035m, 847m, 636w. MS (ESI+): 404.21 (75, [M+H]⁺), 426.22 (81, [M+Na]⁺), 829.38 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₃H₃₃NaNO₅ ([M+Na]⁺) 426.2251 found 426.2247.

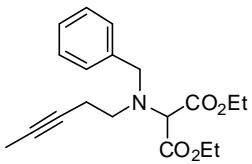
Diethyl 2-(benzyl(pent-4-ynyl)amino)malonate 10



According to GP2 *N*-benzylpent-4-yn-1-amine (4.11 g, 23.7 mmol, 1.5 eq.), diethyl 2-bromomalonate (92% pure, 2.93 mL, 15.8 mmol, 1.0 eq.) and NEt₃ (4.40 mL, 31.6 mmol, 2.0 eq.) were heated at reflux in CHCl₃ (100 mL) for 3 d. Purification by FC (PE/Et₂O 5:1, R_f (DCM) = 0.70) afforded diethyl 2-(benzyl(pent-4-ynyl)amino)malonate 10 (2.32 g, 7.0 mmol, 44%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.40-7.36 (*m*, 2H, H_{ar}), 7.34-7.29 (*m*, 2H, H_{ar}), 7.27-7.21 (*m*, 1H, H_{ar}), 4.24 (*q*, 4H, *J* = 7.1 Hz, 2×CH₂O), 4.19 (*s*, 1H, CH(CO)₂), 3.87 (*s*, 2H, CH₂Ph), 2.83 (*t*, 2H, *J* = 7.1 Hz, CH₂N), 2.22 (*dt*, 2H, *J* = 7.1, 2.6 Hz, CH₂CC), 1.89 (*t*, 1H, *J* = 2.6 Hz, CCH), 1.70 (*qn*, 2H, *J* = 7.1 Hz, CH₂CH₂CH₂), 1.30 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.2 (2×CO), 139.2 (C_{ar}), 128.7 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.1 (CH_{ar}), 84.4 (C_{sp}), 68.2 (CH_{sp}), 66.5 (CH), 61.3 (2×CH₂), 56.0 (CH₂), 50.7 (CH₂), 27.3 (CH₂), 15.9 (CH₂), 14.2 (2×CH₃). IR (film): 3291s, 3063w, 3029w, 2982m, 2939w, 2848w, 2117w, 1733s, 1495w, 1454m, 1379m, 1302m, 1227m, 1175m, 1145s, 1030s, 861w, 739m, 699m, 638m. MS (ESI+): 332.20 (23, [M+H]⁺), 340.18 (98), 354.17 (67, [M+Na]⁺), 511.26 (100), 542.33 (55), 686.34 (53, [2M+Na]⁺). HRMS (ESI): calculated for C₁₉H₂₅NaNO₄ ([M+Na]⁺) 354.1676 found 354.1665.

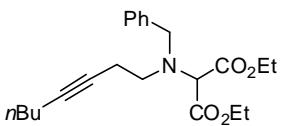
Diethyl 2-(benzyl(pent-3-ynyl)amino)malonate 12a



According to GP2 *N*-benzylpent-3-yn-1-amine (2.98 g, 17.2 mmol, 1.5 eq.), diethyl 2-bromomalonate (92% pure, 2.62 mL, 11.5 mmol, 1.0 eq.) and NEt₃ (3.20 mL, 23.0 mmol, 2.0 eq.) were heated at reflux in CHCl₃ (100 mL) for 3 d. Purification by FC (PE/Et₂O 5:1, R_f (PE/Et₂O 3:1) = 0.36) afforded diethyl 2-(benzyl(pent-3-ynyl)amino)malonate **12a** (3.53 g, 10.6 mmol, 93%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.41-7.39 (*m*, 2H, H_{ar}), 7.33-7.29 (*m*, 2H, H_{ar}), 7.27-7.23 (*m*, 1H, H_{ar}), 4.24 (*q*, 4H, *J* = 7.0 Hz, 2×CH₂O), 4.23 (*s*, 1H, CH), 3.93 (*s*, 2H, CH₂Ph), 2.92 (*t*, 2H, *J* = 7.5 Hz, CH₂N), 2.29 (*tq*, 2H, *J* = 7.5, 2.4 Hz, CH₂CC), 1.75 (*t*, 3H, *J* = 2.5 Hz, CH₃CC), 1.29 (*t*, 6H, *J* = 7.0 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (CO), 139.2 (C_{ar}), 128.6 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.1 (CH_{ar}), 77.1 (C_{sp}), 76.5 (C_{sp}), 67.0 (C), 61.3 (2×CH₂), 56.2 (CH₂), 51.6 (CH₂), 19.2 (CH₂), 14.2 (2×CH₃), 3.4 (CH₃). IR (film): 2982m, 2920w, 2855w, 1733s, 1494w, 1453m, 1370m, 1301m, 1221m, 1150s, 1075w, 1029s, 740m, 698m. MS (ESI+): 332.18 (58, [M+H]⁺), 354.14 (77, [M+Na]⁺), 685.29 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₁₉H₂₅NaNO₄ ([M+Na]⁺) 354.1676 found 354.1673.

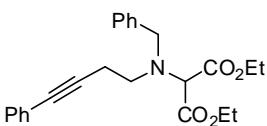
Diethyl 2-(benzyl(oct-3-ynyl)amino)malonate 12b



According to GP2 *N*-benzyloct-3-yn-1-amine (2.58 g, 12.0 mmol, 1.2 eq.), diethyl 2-bromomalonate (92% pure, 1.83 mL, 9.9 mmol, 1.0 eq.) and NEt₃ (16.0 mmol, 2.23 mL, 1.6 eq.) were heated at reflux in CHCl₃ (100 mL) for 3 d. Purification by FC (PE/Et₂O 6:1) afforded diethyl 2-(benzyl(oct-3-ynyl)amino)malonate **12b** (2.19 g, 5.9 mmol, 59%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.40-7.30 (*m*, 2H, H_{ar}), 7.32-7.28 (*m*, 2H, H_{ar}), 7.26-7.22 (*m*, 1H, H_{ar}), 4.25 (*s*, 1H, CH(CO)₂), 4.23 (two *q*, 4H, *J* = 7.1 Hz, 2×CH₂O), 3.94 (*s*, 2H, CH₂Ar), 2.92 (*t*, 2H, *J* = 7.3 Hz, CH₂N), 2.32 (*tt*, 2H, *J* = 7.4, 2.3 Hz, nPrCH₂CC), 2.10 (*tt*, 2H, *J* = 7.3, 2.3 Hz, nBuCCCH₂), 1.46-1.32 (*m*, 4H, CH₃CH₂CH₂CH₂), 1.29 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃), 0.88 (*t*, 3H, *J* = 7.2 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (2×CO), 139.2 (C_{ar}), 128.6 (2×CH_{ar}), 128.2 (2×CH_{ar}), 127.1 (CH_{ar}), 81.3 (C), 77.9 (C), 66.9 (CH), 61.2 (2×CH₂), 56.2 (CH₂), 51.6 (CH₂), 31.1 (CH₂), 21.9 (CH₂), 19.3 (CH₂), 18.4 (CH₂), 14.1 (2×CH₃), 13.6 (CH₃). IR (film): 3086w, 3063w, 3028w, 2980m, 2959m, 2933m, 2861m, 1735s, 1494w, 1454m, 1370m, 1301m, 1220s, 1149s, 1029s, 862w, 740m, 698m. MS (ESI+): 374.25 (30, [M+H]⁺), 396.22 (100, [M+Na]⁺), 769.46 (22, [2M+Na]⁺). HRMS (ESI): calculated for C₂₂H₃₁NaNO₄ ([M+Na]⁺) 396.2145 found 396.2141.

Diethyl 2-(benzyl(4-phenylbut-3-ynyl)amino)malonate 12c

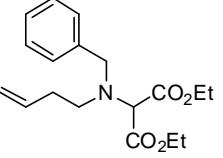


According to GP2 *N*-benzyl-4-phenylbut-3-yn-1-amine (1.41 g, 6.0 mmol, 1.5 eq.), 5.92 mL diethyl 2-bromomalonate (92% pure, 4.0 mmol, 1.0 eq.) and NEt₃ (1.11 mL, 8.0 mmol, 2.0 eq.) were heated at reflux in CHCl₃ (50 mL) for 3 d. Purification by FC (PE/Et₂O 6:1) afforded diethyl 2-(benzyl(4-phenylbut-3-ynyl)amino)malonate **12c** (1.06 g, 2.7 mmol, 67%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.45-7.43 (*m*, 2H, H_{ar}), 7.38-7.24 (*m*, 8H, H_{ar}), 4.29 (*s*, 1H, CH), 4.28-4.20 (*m*, 4H, 2×CH₂O), 4.00 (*s*, 2H, CH₂Ph), 3.07 (*t*, 2H, *J* = 7.3 Hz, CH₂N), 2.59 (*t*, 2H, *J* = 7.3 Hz, CH₂CC), 1.29 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (2×CO), 139.1 (C_{ar}), 131.5 (2×CH_{ar}), 128.6 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.2 (2×CH_{ar}), 127.6 (CH_{ar}), 127.2 (CH_{ar}), 123.8 (C_{ar}), 88.2 (C),

81.5 (C), 67.0 (CH), 61.4 (2×CH₂), 56.3 (CH₂), 51.2 (CH₂), 20.0 (CH₂), 14.2 (2×CH₃). IR (film): 3061w, 3028w, 2981m, 2936w, 2905w, 2850w, 1732s, 1491w, 1253w, 1370w, 1229m, 1174w, 1147m, 1028m, 757m, 693w, 668m. MS (ESI+): 394.20 (32, [M+H]⁺), 416.18 (100, [M+Na]⁺). HRMS (ESI): calculated for C₂₄H₂₇NaNO₄ ([M+Na]⁺) 416.1832 found 416.1832.

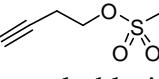
Diethyl 2-(benzyl(but-3-enyl)amino)malonate **14**



According to GP2 *N*-benzylbut-3-en-1-amine (5.32 g, 33.0 mmol, 1.5 eq.), diethyl 2-bromomalonate (92% pure, 5.03 mL, 22.0 mmol, 1.0 eq.) and NEt₃ (44.0 mmol, 6.13 mL, 2.0 eq.) were heated at reflux in CHCl₃ (150 mL) for 3 d. Purification by FC (PE/Et₂O 5:1) afforded diethyl 2-(benzyl(but-3-enyl)amino)malonate **14** (5.56 g, 17.4 mmol, 79%) as a yellow oil.
¹H-NMR (400 MHz, CDCl₃): 7.41-7.39 (*m*, 2H, H_{ar}), 7.34-7.30 (*m*, 2H, H_{ar}), 7.27-7.22 (*m*, 1H, H_{ar}), 5.79 (*ddt*, 1H, *J* = 17.0, 10.2, 6.8 Hz, H_{olef}), 5.03 (*ddd*, 1H, *J* = 17.3, 3.5, 1.6 Hz, H_{olef}), 4.98 (*tdd*, 1H, *J* = 10.2, 2.1, 1.6 Hz, H_{olef}), 4.23 (*q*, 4H, *J* = 7.1 Hz, 2×CH₂O), 4.21 (*s*, 1H, CH), 3.89 (*s*, 2H, CH₂Ph), 2.81 (*t*, 2H, *J* = 7.1 Hz, CH₂N), 2.28-2.23 (*m*, 2H, CH₂C=C), 1.29 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (2×CO), 139.3 (C_{ar}), 136.4 (CH_{olef}), 128.7 (2×CH_{ar}), 128.2 (2×CH_{ar}), 127.1 (CH_{ar}), 115.7 (CH_{2olef}), 66.5 (CH), 61.2 (2×CH₂), 55.9 (CH₂), 51.3 (CH₂), 33.0 (CH₂), 14.2 (2×CH₃). IR (film): 2981m, 2937w, 2907w, 2850w, 1734s, 1640w, 1494w, 1453m, 1369m, 1301m, 1221m, 1152m, 1029s, 913w, 740m, 698m. MS (ESI+): 320.17 (96, [M+H]⁺), 342.16 (96, [M+Na]⁺), 661.30 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₁₈H₂₅NaNO₄ ([M+Na]⁺) 342.1676 found 342.1673.

1. 3. Synthesis of carbamate protected alkynyl amino malonates

But-3-ynyl methanesulfonate

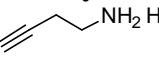


To a mixture of but-3-yn-1-ol (18.89 mL, 250 mmol, 1.0 eq.) and NEt₃ (52.23 mL, 375 mmol, 1.5 eq.) in DCM (250 mL) at 0 °C was added mesyl chloride (19.35 mL, 250 mmol, 1.0 eq.) dropwise over 30 min. After addition the reaction was stirred at RT for 2 h. Then water (200 mL) was added and the organic layer was separated, washed with 1 M HCl, sat. NaHCO₃ sol. and brine and dried (MgSO₄). After evaporation of the solvent but-3-ynyl methanesulfonate (33.42 g, 225 mmol, 90%) was obtained as a yellow oil which was used in the next step without further purification.

¹H-NMR (400 MHz, CDCl₃): 4.31 (*t*, 2H, *J* = 6.7 Hz, CH₂O), 3.06 (*s*, 3H, CH₃), 2.66 (*td*, 2H, *J* = 6.7, 2.7 Hz, CH₂CC), 2.07 (*t*, 1H, *J* = 2.7 Hz, CCH).

The ¹H-NMR data is in accordance with the literature.^[15]

But-3-yn-1-amine hydrochloride



via the azide: To but-3-ynyl 4-methylbenzenesulfonate (10.02 g, 44 mmol, 1.0 eq.) in DMF (60 mL) was added NaN₃ (14.5 g, 223 mmol, 5.0 eq.) and the resulting solution was stirred for 40 h at RT. Then Et₂O (200 mL) and water (200 mL) were added and the organic layer separated. The aqueous layer was extracted with Et₂O (200 mL) and the combined organic layers washed with water (5×100 mL). The organic layers were dried (Na₂SO₄), PPh₃ (13.0 g, 10.2 mmol, 1.0 eq.) was added and the reaction stirred at RT for 40 h. The reaction was quenched by addition of water (20 mL) and was stirred for 2 h at RT. Then it was dried (Na₂SO₄)

cooled to 0 °C and filtered. The solution was diluted with PE (600 mL), cooled to - 20 °C and filtered to remove the phosphine oxide. The solution was warmed to RT and treated with HCl in Et₂O (approx. 2.5 M) to pH 1 to precipitate the amine hydrochloride. This was collected by filtration and dried in vacuum to give but-3-yn-1-amine hydrochloride (2.55 g, 24.4 mmol, 41%) as a white solid which was used in the next step without further purification.

via the phthalimide: To potassium phthalimide (58.03 g, 313 mmol, 1.0 eq.) and NaI (5.14 g, 31 mmol, 0.1 eq.) in DMF (800 mL) was added but-3-ynyl 4-methanesulfonate (48.74 g, 329 mmol, 1.05 eq.) dropwise over 10 min. After complete addition the reaction was heated to 100 °C for 4 h. After cooling, water (1200 mL) was added and the solution filtered. After drying the 2-(but-3-ynyl)isoindoline-1,3-dione (48.65 g, 244 mmol, 78%) was obtained as a white solid which was used without further purification.

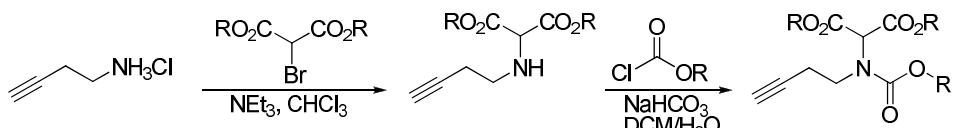
2-(But-3-ynyl)isoindoline-1,3-dione (48.65 g, 244 mmol, 1.0 eq.) was suspended in EtOH (1800 mL) and hydrazine hydrate (17.84 mL, 366 mmol, 1.5 eq.) was added. The reaction was stirred for 3 d at RT over which time a precipitate appeared and the mixture became very thick. Water (1800 mL) was then added and all solids dissolved. After addition of conc. hydrochloric acid (75 mL) the reaction was stirred for 15 h and a white precipitate appeared again, which was filtered off (phthaloyl hydrazide). The filtrate was freed from ethanol and made basic by addition of NaOH (40 g). The aqueous layer was then extracted 16× with Et₂O and the organic layer was treated with anhydrous HCl to precipitate the amine hydrochloride. During this process the reaction became cloudy and a second layer appeared. All the volatiles were removed and the oily residue was coevaporated several times with toluene. The solid thus obtained was suspended in PE and collected by filtration and dried in vacuum. The aqueous layer which remained after the extraction process was extracted 8× with DCM. The DCM layers were combined and treated with anhydrous HCl. A precipitate appeared which was collected by filtration and dried in vacuum giving but-3-yn-1-amine hydrochloride (14.50 g in total, 137 mmol, 56%) as an off-white white solid.

2-(But-3-ynyl)isoindoline-1,3-dione: ¹H-NMR (400 MHz, CDCl₃): 7.88-7.84 (*m*, 2H, H_{ar}), 7.74-7.72 (*m*, 2H, H_{ar}), 3.89 (*t*, 1H, *J* = 7.1 Hz, CH₂N), 2.62 (*td*, 1H, *J* = 7.1, 2.6 Hz, CH₂CC), 1.96 (*t*, 1H, *J* = 2.6 Hz, CCH).

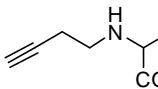
The ¹H-NMR data is in accordance to the literature.^[7]

But-3-yn-1-amine hydrochloride: ¹H-NMR (400 MHz, D₂O): 3.06 (*t*, 2H, *J* = 6.6 Hz, CH₂N), 2.52 (*td*, 2H, *J* = 6.6, 2.7 Hz, CH₂CC), 2.38 (*t*, 1H, *J* = 2.7 Hz, CCH).

The protons at the nitrogen are not visible. The ¹H-NMR data is in accordance with the literature.^[16]

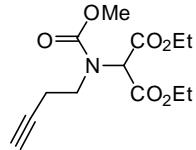


Diethyl 2-(but-3-ynylamino)malonate

 To but-3-yn-1-amine hydrochloride (1.22 g, 11.6 mmol, 1.5 eq.) in CHCl₃ (20 mL) was added diethyl 2-bromomalonate (92% pure, 1.84 mL, 7.7 mmol, 1.0 eq.) and NEt₃ (2.68 mL, 19.3 mmol, 2.5 eq.). The reaction mixture was heated at 60 °C in a sealed tube for 15 h. Then 1 M NaOH and EtOAc were added and the organic layer was separated. The aqueous layer was extracted 3× with EtOAc the organic layers combined, washed with water, brine and dried (MgSO₄). The solvent was evaporated and FC (PE/EtOAc 4:1) gave diethyl 2-(but-3-ynylamino)malonate (612 mg, 2.7 mmol, 35%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 4.24 (*two q*, 4H, *J* = 7.2 Hz, 2×CH₂O), 4.08 (s, 1H, CHN), 2.79 (*t*, 2H, *J* = 6.8 Hz, CH₂N), 2.40 (*td*, 2H, *J* = 6.8, 2.6 Hz, CH₂CC), 2.34 (s, 1H, NH), 2.01 (*t*, 1H, *J* = 2.6 Hz, CCH), 1.28 (*t*, 6H, *J* = 7.2 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (2×CO), 81.7 (C_{sp}), 69.9 (CH_{sp}), 64.9 (CH), 61.9 (2×OCH₂), 46.2 (CH₂N), 19.8 (CH₂C), 14.1 (2×CH₃). IR(film): 3287m, 2984m, 2939w, 1737s, 1468w, 1369m, 1212m 1155m, 1095w, 1027m, 860w, 649w. MS (ESI+): 228.1 (82 , [M+H]⁺), 250.1 (51 , [M+Na]⁺), 477.2 (100 , [2M+Na]⁺). HRMS (ESI): calculated for C₁₁H₁₈NO₄ ([M+H]⁺) 228.1236, found 228.1230.

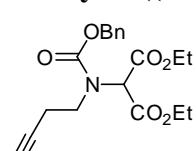
Dimethyl 2-(but-3-ynyl(methoxycarbonyl)amino)malonate 7d



Diethyl 2-(but-3-ynylamino)malonate (227 mg, 1.0 mmol, 1.0 eq.) and NaHCO₃ (252 mg, 3.0 mmol, 3.0 eq.) were suspended in DCM (5 mL). Methyl chloroformate (86 μL, 1.1 mmol, 1.1 eq.) was added dropwise and the reaction was stirred at RT for 15 h. Then it was filtered over silica (eluent: Et₂O) and the solvent was evaporated. Purification by FC (PE/Et₂O 1:1) afforded dimethyl 2-(but-3-ynyl(methoxycarbonyl)amino)malonate **7d** (226.4 mg, 0.79 mmol, 79%) as a colorless oil.

Mixture of rotamers: ¹H-NMR (400 MHz, CDCl₃): 5.32 (s, 0.61H, CH), 5.05 (s, 0.39H, CH), 4.32-4.19 (m, 4H, 2×OCH₂), 3.77 (s, 1.83H, CH₃), 3.69 (s, 1.17H, CH₃), 3.54-3.48 (m, 2H, CH₂N), 2.56-2.49 (m, 2H, CH₂CC), 1.98-1.96 (m, 1H, CCH), 1.30 (t, 6H, *J* = 7.2 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 166.4/166.2 (2×CO), 156.8/155.7 (CO), 81.4/81.2 (C), 69.8/69.7 (CH), 63.5/63.0 (CH), 62.2 (2×CH₂), 53.5/53.1 (CH₃), 47.4/46.2 (CH₂), 19.0/18.4 (CH₂), 14.0 (2×CH₃). IR (film): 3284m, 2984m, 2961w, 1742s, 1713s, 1471m, 1444w, 1407w, 1369w, 1299s, 1264m, 1184s, 1029s, 775w, 643w. MS (ESI+): 286.13 (25, [M+H]⁺), 308.10 (85, [M+Na]⁺), 593.15 (98, [2M+Na]⁺), 607.21 (100, [2M-2H+K]). HRMS (ESI): calculated for C₁₃H₁₉NNaO₆ ([M+Na]⁺) 308.1105, found 308.1110.

Diethyl 2-((benzyloxycarbonyl)(but-3-ynyl)amino)malonate 7e

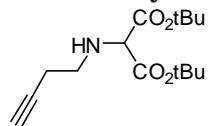


Diethyl 2-(but-3-ynylamino)malonate (455 mg, 2.0 mmol, 1.0 eq.) was dissolved in DCM (4 mL) and sat. NaHCO₃ sol. (4 mL) was added. To the vigorously stirred solution was added dropwise benzyl chloroformate (430 μL, 3.0 mmol, 1.5 eq.). After complete addition the reaction was stirred at RT and monitored by TLC. After 30 min the TLC indicated complete conversion, the reaction was filtered over silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 2:1) afforded diethyl 2-((benzyloxycarbonyl)(but-3-ynyl)amino)malonate **7e** (599.1 mg, 1.66 mmol, 83%) as a clear oil.

Mixture of rotamers: ¹H-NMR (400 MHz, CDCl₃): 7.38-7.30 (m, 5H, H_{ar}), 5.33 (s, 1.17H, CH₂Ar), 5.21 (s, 0.59H, CH), 5.14 (s, 0.83H, CH₂Ar), 5.04 (s, 0.41H, CH), 4.32-4.13 (m, 4H, 2×CH₂), 3.59-3.54 (m, 2H, CH₂N), 2.59-2.51 (m, 2H, CH₂CC), 1.98-1.96 (m, 1H, CCH), 1.30, (t, 2.36H, *J* = 7.1 Hz, 2×CH₃), 1.22 (1.64H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃, RT): 166.4/166.1 (CO), 156.2/155.1 (CO), 135.9/135.8 (C_{ar}), 128.6/128.4 (2×CH_{ar}), 128.2/128.2 (CH_{ar}), 128.1/127.9 (2×CH_{ar}), 81.4/81.2 (C_{sp}), 69.9/69.9 (CH_{sp}), 68.1/67.9 (CH), 63.7/63.2 (CH₂Ar), 62.2/62.2 (2×CH₂), 47.7/46.4 (CH₂), 19.1/18.4 (CH₂), 14.0/13.9 (2×CH₃). IR (film): 3287m, 2983m, 1741m 1711s, 1466m, 1417m, 1369m, 1293s, 1261m, 1183s, 1026s, 771w, 698w. MS (ESI+): 362.17 (22, [M+H]⁺), 384.15 (30, [M+Na]⁺), 420.20 (77), 464.27

(82), 745.22 (100, [2M+Na]⁺) HRMS (ESI): calculated for C₁₉H₂₃NNaO₆ ([M+Na]⁺) 384.1418, found 384.1418.

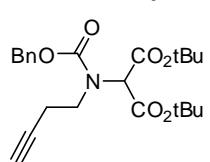
Di-*tert*-butyl 2-(but-3-ynylamino)malonate



Butynyl amine hydrochloride (4.59 g, 43.5 mmol, 1.5 eq.) was suspended in CHCl₃ (200 mL). Then di-*tert*-butyl 2-bromomalonate (8.55 g, 29.0 mmol, 1.0 eq.) and NEt₃ (12.11 mL, 87.0 mmol, 3.0 eq.) were added and the reaction was heated to 80 °C for 6 h. Water (200 mL) was added and the layers were separated. The aqueous layer was extracted 2× with DCM and all organic layers were combined, dried (MgSO₄) and the solvent evaporated. The residue was purified by FC (PE/Et₂O 2:1) to give di-*tert*-butyl 2-(but-3-ynylamino)malonate (1.87 g, 6.6 mmol, 23%) as a slightly yellow oil. Additionally di-*tert*-butyl 2-bromomalonate (5.41 g, 18.3 mmol, 63%) was isolated.

¹H-NMR (400 MHz, CDCl₃): 3.88 (*s*, 1H, CHN), 2.78 (*t*, 2H, *J* = 6.8 Hz, CH₂N), 2.41 (*dt*, 2H, *J* = 6.8, 2.6 Hz, CH₂CC), 2.26 (*bs*, 1H, NH), 2.01 (*t*, 1H, *J* = 2.6 Hz, CCH), 1.48 (*s*, 18H, 2×C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃): 167.6 (2×CO), 82.2 (2×C_{sp3}), 81.9 (C_{sp}), 69.6 (CH_{sp3}), 66.2 (CH_{sp}), 45.9 (CH₂), 27.8 (6×CH₃), 19.8 (CH₂). IR (film): 3292s, 2979s, 2935m, 1732s, 1475m, 1459m, 1393m, 1369s, 1329m, 1293m, 1249s, 1147s, 973w, 949w, 848s, 796m. MS (ESI+): 284.17 (73, [M+H]⁺). HRMS (ESI): calculated for C₁₅H₂₆NO₄ ([M+H]⁺) 284.1856, found 284.1864.

Di-*tert*-butyl 2-((benzyloxycarbonyl)(but-3-ynyl)amino)malonate 7f



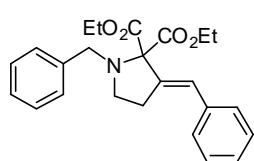
Di-*tert*-butyl 2-(but-3-ynylamino)malonate (566 mg, 2.0 mmol, 1.0 eq.) was dissolved in DCM (4 mL) and sat. NaHCO₃ sol. (4 mL) was added. To this mixture was then added benzyl chloroformate (430 μL, 3.0 mmol, 1.5 eq.) and the reaction was stirred at RT. The progress was monitored by TLC which indicated complete conversion after 30 min. The mixture was filtered over silica (eluent: Et₂O) and the solvent was then removed. The crude product was purified by FC (PE/Et₂O 4:1, R_f (PE/Et₂O 1:1) = 0.61), affording di-*tert*-butyl 2-((benzyloxycarbonyl)(but-3-ynyl)amino)malonate **7f** (766.1 mg, 1.83 mmol, 92%) as a colorless oil.

Mixture of rotamers: ¹H-NMR (400 MHz, CDCl₃): 7.40-7.30 (*m*, 5H, H_{ar}), 5.20-5.19 (*m*, 1.68H, CH₂Ar/CHN), 5.14 (*s*, 0.89H, CH₂Ar), 4.95 (*s*, 0.43H, CHN), 3.57-3.53 (*m*, 2H, CH₂N), 2.61-2.52 (*m*, 2H, CH₂CC), 1.98-1.96 (*s*, 1H, CCH), 1.50 (*s*, 10H, C(CH₃)₃), 1.44 (*s*, 8H, C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃): 165.6/165.3 (CO), 156.2/155.4 (CO), 136.1/136.0 (C_{ar}), 128.6/128.4 (CH_{ar}), 128.2/128.1 (CH_{ar}), 127.9 (2×CH_{ar}), 83.1 (2×C), 81.5/81.3 (C_{sp}), 69.8/69.7 (CH_{sp}), 67.9/67.8 (C), 64.9/64.4 (CH₂), 47.1/46.0 (CH₂), 27.9/27.8 (6×CH₃), 19.3/18.5 (CH₂). IR (film): 3292w, 2979m, 1733s, 1712s, 1498w, 1456w, 1369m, 1292m, 1255m, 1144s, 992w, 847w, 784w, 740w, 697w. MS (ESI+): 440.22 (31, [M+Na]⁺), 476.27 (66), 520.32 (76), 857.33 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₃H₃₁NNaO₆ ([M+Na]⁺) 440.2044, found 440.2036.

2. Cyclization reactions

2. 1. Cyclization of terminal alkynyl amino malonates

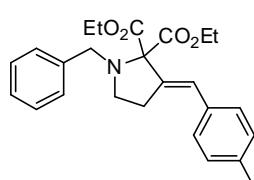
(E)-Diethyl 1-benzyl-3-benzylidenepyrrolidine-2,2-dicarboxylate 5a



Pd(dppf)Cl₂ (20 mg, 25 µmol, 2.5 mol%) and CuI (10 mg, 50 µmol, 5.0 mol%) were suspended in THF (2 mL) and iodobenzene (170 µl, 1.5 mmol, 1.5 eq.) was added. In a separate flask, diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) was dissolved in THF (2 mL) and treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM, R_f (DCM) = 0.46) afforded (E)-diethyl 1-benzyl-3-benzylidenepyrrolidine-2,2-dicarboxylate **5a** (300.5 mg, 0.76 mmol, 76%) as a clear oil.

¹H-NMR (400 MHz, CDCl₃): 7.44-7.42 (*m*, 2H, H_{ar}), 7.34-7.31 (*m*, 6H, H_{ar}), 7.28-7.23 (*m*, 2H, H_{ar}), 6.80 (*t*, 1H, *J* = 2.4 Hz, H_{olef}), 4.35 (*dq*, 2H, *J* = 10.7, 7.1 Hz, OCHH), 4.29 (*dq*, 2H, *J* = 10.7, 7.1 Hz, OCHH), 3.93 (*s*, 2H, CH₂Ph), 2.96-2.93 (*m*, 2H, CH₂N), 2.86-2.82 (*m*, 2H, CH₂C=C), 1.33 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.2 (2×CO), 139.9 (C_{ar}), 139.5 (C_{ar}), 137.2 (C_{olef}), 128.7 (2×CH_{ar}), 128.5 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.0 (CH_{ar}), 127.0 (CH_{ar}), 126.0 (CH_{olef}), 78.9 (C(CO)₂), 61.5 (2×OCH₂), 54.6 (CH₂Ph), 50.1 (CH₂N), 30.2 (CH₂), 14.3 (2×CH₃). IR(film): 3061w, 3027w, 2980m, 2935w, 2834w, 1729s, 1494w, 1448m, 1368w, 1229s, 1139w, 1041m, 742w, 697m. MS (ESI+): 394 (100, [M+H]⁺). HRMS (ESI): calculated for C₂₄H₂₈NO₄ ([M+H]⁺) 394.2013, found 394.2011.

(E)-Diethyl 1-benzyl-3-(4-methylbenzylidene)pyrrolidine-2,2-dicarboxylate 5b



Pd(dppf)Cl₂ (20 mg, 25 µmol, 2.5 mol%) and CuI (10 mg, 50 µmol, 5.0 mol%) were suspended in THF (2 mL) and 4-iodotoluene (327 mg, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM, R_f (DCM) = 0.46) afforded (E)-diethyl 1-benzyl-3-(4-methylbenzylidene)pyrrolidine-2,2-dicarboxylate **5b** (297.8 mg, 0.73 mmol, 73%) as a clear oil.

¹H-NMR (400 MHz, CDCl₃): 7.47-7.13 (*m*, 9H, H_{ar}), 6.77 (*t* 1H, *J* = 2.5 Hz, H_{olef}), 4.39-4.25 (*m*, 4H, 2×OCH₂), 3.94 (*s*, 2H, CH₂Ph), 2.96-2.93 (*m*, 2H, CH₂N), 2.84-2.81 (*m*, 2H, CH₂C=C), 2.35 (*s*, 3H, ArCH₃), 1.34 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.3 (2×CO), 139.5 (C_{ar}), 138.9 (C_{ar}), 136.9 (C_{ar}), 134.9 (C_{olef}), 129.0 (2×CH_{ar}), 128.6 (2×CH_{ar}), 128.5 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.0 (CH_{ar}), 125.8 (CH_{olef}), 78.8 (C), 61.5 (2×CH₂), 54.6 (CH₂), 50.2 (CH₂), 30.1 (CH₂),

21.2 (CH₃), 14.3 (2×CH₃). IR (film): 3029w, 2980m, 2930w, 2832w, 1728s, 1512w, 1495w, 1453w, 1367w, 1250s, 1229s, 1168w, 1137m, 1041m, 814w, 743w, 700w. MS (ESI+): 408.3 (100, [M+H]⁺), 837.3 (58, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₂₉NNaO₄ ([M+Na]⁺) 430.1989, found 430.1980.

(E)-Diethyl 1-benzyl-3-(2-methylbenzylidene)pyrrolidine-2,2-dicarboxylate 5c

Pd(dppf)Cl₂ (20 mg, 25 μmol, 2.5 mol%) and CuI (10 mg, 50 μmol, 5.0 mol%) were suspended in THF (2 mL) and 2-iodotoluene (192 μL, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM, R_f (DCM) = 0.40) afforded (E)-diethyl 1-benzyl-3-(2-methylbenzylidene)pyrrolidine-2,2-dicarboxylate **5c** (277.0 mg, 0.68 mmol, 68%) as a clear yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.45 (*d*, 2H, *J* = 7.2 Hz, H_{ar}), 7.34 (*t*, 2H, *J* = 7.4 Hz, H_{ar}), 7.28-7.25 (*m*, 2H, H_{ar}), 7.21-7.16 (*m*, 3H, H_{ar}), 6.91 (*t*, 1H, *J* = 2.5 Hz, H_{olef}), 4.40-4.28 (*m*, 4H, 2×CH₂O), 3.98 (*s*, 2H, CH₂Ph), 2.90 (*t*, 2H, *J* = 6.6 Hz, CH₂N), 2.66 (*td*, 2H, *J* = 6.6 2.5 Hz, CH₂C=C), 2.29 (*s*, 3H, CH₃Ar), 1.36 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.4 (2×CO), 140.5 (C_{ar}), 139.6 (C_{ar}), 136.4 (C_{ar}), 136.3 (C_{olef}), 129.9 (CH_{ar}), 128.5 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.0 (CH_{ar}), 127.2 (CH_{ar}), 127.0 (CH_{ar}), 125.6 (CH_{ar}), 124.8 (CH_{olef}), 78.4 (C), 61.5 (2×CH₂), 54.7 (CH₂), 50.0 (CH₂), 29.5 (CH₂), 19.8 (CH₃), 14.3 (2×CH₃). IR (film): 2980m, 1730s, 1455w, 1367w, 1250m, 1230m, 1165w, 1137m, 1042m, 744m, 699w. MS (ESI+): 408.3 (100, [M+H]⁺), 837.3 (18, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₂₉NNaO₄ ([M+Na]⁺) 430.1989, found 430.1995.

(E)-Diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzylidene)pyrrolidine-2,2-dicarboxylate 5d

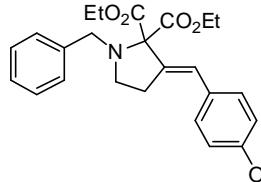
Pd(dppf)Cl₂ (20 mg, 25 μmol, 2.5 mol%) and CuI (10 mg, 50 μmol, 5.0 mol%) were suspended in THF (2 mL) and methyl 4-iodobenzoate (393 mg, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS

(1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (PE/Et₂O 4:1, R_f (PE/Et₂O 2:1) = 0.49) afforded (E)-diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzylidene)-pyrrolidine-2,2-dicarboxylate **5d** (316.9 mg, 0.70 mmol, 70%) as a white crystalline solid; mp 69.1 °C.

¹H-NMR (400 MHz, CDCl₃): 8.01 (*d*, 2H, *J* = 8.4 Hz, H_{ar}), 7.44-7.38 (*m*, 4H, H_{ar}), 7.34 (*t*, 2H, *J* = 7.3 Hz, H_{ar}), 7.28-7.25 (*m*, 1H, H_{ar}), 6.85 (*t*, 1H, *J* = 2.3 Hz, C=CH), 4.41-4.29 (*m*, 4H, CH₂O), 3.95 (*s*, 2H, CH₂Ar), 3.92 (*s*, 3H, OCH₃), 2.96 (*t*, 2H, *J* = 6.5 Hz, CH₂N), 2.86 (*td*, 2H, *J* = 6.9, 3.4 Hz, CH₂C=C), 1.34 (*t*, 6H, *J* = 7.1 Hz,

$2\times\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3): 168.9 ($2\times\text{CO}$), 166.8 (CO), 142.6 (C_{ar}), 141.7 (C_{ar}), 139.3 (C_{olef}), 129.6 ($2\times\text{CH}_{\text{ar}}$), 128.5 ($2\times\text{CH}_{\text{ar}}$), 128.5 ($2\times\text{CH}_{\text{ar}}$), 128.4 (C_{ar}), 128.3 ($2\times\text{CH}_{\text{ar}}$), 127.1 (CH_{ar}), 125.2 (CH_{olef}), 79.0 (C), 61.7 ($2\times\text{CH}_2$), 54.6 (CH_2), 52.1 (CH_3), 50.0 (CH_2), 30.3 (CH_2), 14.3 ($2\times\text{CH}_3$). IR (film): 2980m, 2835w, 1722s, 1606w, 1413w, 1279s, 1251w, 1229w, 1110m, 1041m, 772w, 744w, 699m. MS (ESI+): 452.18 (98, $[\text{M}+\text{H}]^+$), 474.18 (69, $[\text{M}+\text{Na}]^+$), 553.31 (78), 734.42 (75), 925.31 (100, $[\text{M}+\text{Na}]^+$). HRMS (ESI): calculated for $\text{C}_{26}\text{H}_{30}\text{NO}_6$ ($[\text{M}+\text{H}]^+$) 452.2068, found 452.2069.

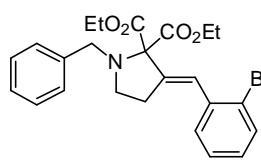
(E)-Diethyl 1-benzyl-3-(4-methoxybenzylidene)pyrrolidine-2,2-dicarboxylate 5e



$\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mg, 25 μmol , 2.5 mol%) and CuI (10 mg, 50 μmol , 5.0 mol%) were suspended in THF (2 mL) and 4-methoxyiodobenzene (351 mg, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzylbut-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et_2O) and the solvent evaporated. Purification by FC (DCM, R_f (DCM) = 0.26) afforded an inseparable mixture of (E)-diethyl 1-benzyl-3-(4-methoxybenzylidene)pyrrolidine-2,2-dicarboxylate **5e** and diethyl 1-benzyl-3-methylenepyrrolidine-2,2-dicarboxylate **6** (10:1, 314.5 mg), (0.69 mmol, 69% and 0.07 mmol, 7%) as a clear yellow oil. An analytical sample was obtained by semi-preparative HPLC.

^1H -NMR (400 MHz, CDCl_3): 7.45-7.43 (*m*, 2H, H_{ar})gg, 7.35-7.31 (*m*, 2H, H_{ar}), 7.29-7.24 (*m*, 3H, H_{ar}), 6.90-6.87 (*m*, 2H, H_{ar}), 6.74 (*t*, 1H, J = 2.4 Hz, H_{olef}), 4.39-4.25 (*m*, 4H, $2\times\text{OCH}_2$), 3.94 (*s*, 2H, CH_2Ar), 3.82 (*s*, 3H, OCH_3), 2.95 (*t*, 2H, J = 6.4 Hz, CH_2N), 2.82 (*td*, 2H, J = 6.4, 2.4 Hz, CH_2C), 1.33 (*t*, 6H, J = 7.1 Hz, $2\times\text{CH}_3$). ^{13}C -NMR (125 MHz, CDCl_3): 169.3 (CO), 158.6 (C_{ar}), 139.5 (C_{ar}), 137.6 (C_{olef}), 130.0 (CH_{ar}), 129.9 ($2\times\text{CH}_{\text{ar}}$), 128.5 (CH_{ar}), 128.2 ($2\times\text{CH}_{\text{ar}}$), 127.0 (CH_{ar}), 125.4 (CH_{ar}), 113.7 ($2\times\text{CH}_{\text{ar}}$), 78.8 (C), 61.4 ($2\times\text{CH}_2$), 55.3 (CH_3), 54.6 (CH_2), 50.2 (CH_2), 30.0 (CH_2), 14.3 ($2\times\text{CH}_3$). IR (film): 2979m, 2935w, 2836m, 1727s, 1606m, 1511s, 1455w, 1366w, 1298w, 1250s, 1176w, 1136w, 1037s, 858w, 745w, 700w. MS (ESI+): 424.19 (97, $[\text{M}+\text{H}]^+$), 425.19 (99, $[\text{M}+2\text{H}]^+$), 525.32 (96), 869.36 (100, $[2\text{M}+\text{Na}]^+$). HRMS (ESI): calculated for $\text{C}_{25}\text{H}_{30}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) 424.2118, found 424.2113.

(E)-Diethyl 1-benzyl-3-(2-bromobenzylidene)pyrrolidine-2,2-dicarboxylate 5f

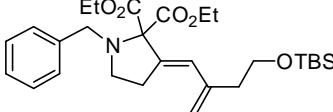


$\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mg, 25 μmol , 2.5 mol%) and CuI (10 mg, 50 μmol , 5.0 mol%) were suspended in THF (2 mL) and 2-bromoiodobenzene (192 μL , 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzylbut-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et_2O) and the solvent evaporated. Purification by FC (DCM, R_f

(DCM) = 0.54) afforded (*E*)-diethyl 1-benzyl-3-(2-bromobenzylidene)pyrrolidine-2,2-dicarboxylate **5f** (302.0 mg, 0.64 mmol, 64%) as a clear yellow oil.

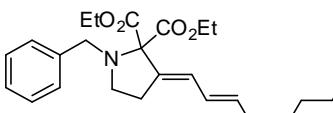
¹H-NMR (400 MHz, CDCl₃): 7.58 (dd, 1H, *J* = 8.0, 1.3 Hz, H_{ar}), 7.46-7.43 (m, 2H, H_{ar}), 7.39-7.24 (m, 5H, H_{ar}), 7.13-7.08 (m, 1H, H_{ar}), 6.98 (t, 1H, *J* = 2.6 Hz, H_{olef}), 4.40-4.29 (m, 4H, 2×CH₂O), 4.00 (s, 2H, CH₂Ph), 2.93 (t, 2H, *J* = 6.5 Hz, CH₂N), 2.70 (dt, 2H, *J* = 6.5, 2.6 Hz, CH₂C=C), 1.37 (t, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.1 (2×CO), 141.9 (C_{ar}), 139.5 (C_{ar}), 137.1 (C_{olef}), 132.7 (CH_{ar}), 129.6 (CH_{ar}), 128.6 (CH_{olef}), 128.5 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.1 (CH_{ar}), 127.0 (CH_{ar}), 125.6 (CH_{ar}), 124.3 (C_{ar}), 78.4 (C), 61.7 (2×CH₂), 54.6 (CH₂), 50.0 (CH₂), 29.6 (CH₂), 14.4 (2×CH₃). IR (film): 2980m, 2934w, 2833m, 1729s, 1494w, 1465m, 1439w, 1389w, 1367w, 1251s, 1137w, 1043m, 1025m, 859w, 744m, 699w. MS (ESI+): 472.1/474.1 (100, [M+H]⁺), 530.2/532.2 (80, [M+NH₄+MeCN]⁺). HRMS (ESI): calculated for C₂₄H₂₆BrNNaO₄ ([M+Na]⁺) 494.0937, found 494.0938.

(*E*)-Diethyl 1-benzyl-3-(4-(*tert*-butyldimethylsilyloxy)-2-methylenebutylidene)-pyrrolidine-2,2-dicarboxylate **5g**

 Pd(dppf)Cl₂ (20 mg, 25 μmol, 2.5 mol%) and CuI (10 mg, 50 μmol, 5.0 mol%) were suspended in THF (2 mL) and *tert*-butyl(3-iodobut-3-enyloxy)dimethylsilane (468 mg, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM, R_f (PE/EtOAc 10:1) = 0.41) afforded (*E*)-diethyl 1-benzyl-3-(4-(*tert*-butyldimethylsilyloxy)-2-methylenebutylidene)-pyrrolidine-2,2-dicarboxylate **5g** (274.5 mg, 0.55 mmol, 55%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.42-7.40 (m, 2H, H_{ar}), 7.34-7.30 (m, 2H, H_{ar}), 7.27-7.23 (m, 1H, H_{ar}), 6.20 (dt, 1H, *J* = 0.8, 2.5 Hz, CH=CR₂), 5.09 (bs, 1H, C=CHH), 5.01 (bs, 1H, C=CHH), 4.32 (dq, 2H, *J* = 10.8, 7.1 Hz, OCH₂), 4.26 (dq, 2H, *J* = 10.8, 7.1 Hz, OCH₂), 3.90 (s, 2H, CH₂Ph), 3.67 (t, 2H, *J* = 7.2 Hz, OCH₂), 2.87 (t, 2H, *J* = 6.6 Hz, CH₂N), 2.68 (dt, 2H, *J* = 6.6, 2.5 Hz, CH₂C=C), 2.38 (t, 2H, *J* = 7.2 Hz, CH₂CH₂O), 1.32 (t, 6H, *J* = 7.1 Hz, 2×CH₃), 0.89 (s, 9H, C(CH₃)₃), 0.05 (s, 6H, Si(CH₃)₂). ¹³C-NMR (100 MHz, CDCl₃): 169.1 (CO), 142.1 (C_{olef}), 139.9 (C_{olef}), 139.5 (CH_{ar}), 128.4 (2×CH_{ar}), 128.2 (2×CH_{ar}), 126.9 (CH_{ar}), 126.5 (CH_{olef}), 116.3 (CH₂olef), 78.5 (C), 62.3 (CH₂O), 61.4 (2×CH₂O), 54.6 (CH₂), 49.9 (CH₂), 40.6 (CH₂), 29.9 (CH₂), 25.9 (3×CH₃), 18.3 (C), 14.3 (2×CH₃), -5.3 (2×CH₃). IR (film): 2955m, 2930m, 2856w, 1730s, 1471w, 1388w, 1366w, 1252s, 1139w, 1096s, 1043m, 836s, 776m, 740w, 699w. MS (ESI+): 502.3 (100, [M+H]⁺), 561.3 (82, [M+tBu+2H]⁺). HRMS (ESI): calculated for C₂₈H₄₄NO₅Si ([M+H]⁺) 502.2983, found 502.2979.

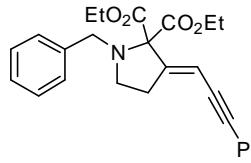
(*E*)-Diethyl 1-benzyl-3-((*E*)-oct-2-enylidene)pyrrolidine-2,2-dicarboxylate **5h**

 Pd(dppf)Cl₂ (10 mg, 12.5 μmol, 2.5 mol%) and CuI (5 mg, 25 μmol, 5.0 mol%) were suspended in THF (1 mL) and (*E*)-1-iodo heptene (168 mg, 0.75 mmol, 1.5 eq.) was added. In a separate flask, a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (159 mg, 0.5 mmol, 1.0 eq.) in THF (1 mL) was treated dropwise with NaHMDS (0.83 mL, 0.6M in toluene, 0.5 mmol, 1.0 eq.).

After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (PE/Et₂O 8:1, R_f (PE/Et₂O 8:1) = 0.3) afforded (*E*)-diethyl 1-benzyl-3-((*E*)-oct-2-enylidene)pyrrolidine-2,2-dicarboxylate **5h** (111.4 mg, 0.27 mmol, 54%) as a clear oil.

¹H-NMR (400 MHz, CDCl₃): 7.42-7.40 (*m*, 2H, H_{ar}), 7.33-7.20 (*m*, 2H, H_{ar}), 7.27-7.23 (*m*, 1H, H_{ar}), 6.33 (*dt*, 1H, J = 10.8, 2.0 Hz, C=CH-CH=CHCH₂), 6.09 (*ddt*, 1H, J = 15.0, 10.8, 1.3 Hz, C=CH-CH=CHCH₂), 5.73 (*dt*, 1H, J = 15.0, 7.1 Hz, C=CH-CH=CHCH₂), 4.32 (*dq*, 2H, J = 10.8, 7.1 Hz, OCH₂), 4.25 (*dq*, 2H, J = 10.8, 7.1 Hz, OCH₂), 3.90 (*s*, 2H, CH₂Ph), 2.88 (*t*, 2H, J = 6.7 Hz, CH₂N), 2.61 (*dt*, 2H, J = 6.7, 2.0 Hz, NCH₂CH₂), 2.10 (*q*, 2H, J = 7.1 Hz, CH=CHCH₂), 1.40 (*qn*, 2H, J = 7.1 Hz, CH₂CH₂CH₂CH₃), 1.31 (*t*, 6H, J = 7.1 Hz, 2×CH₃), 1.34-1.26 (*m*, 4H, CH₂CH₂CH₃), 0.89 (*t*, 3H, J = 6.8 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.2 (2×CO), 139.6 (C_{ar}), 137.1 (C_{olef}), 136.6 (CH_{olef}), 128.5 (2×CH_{ar}), 128.2 (2×CH_{ar}), 126.9 (CH_{ar}), 126.8 (CH_{olef}), 125.4 (CH_{olef}), 77.8 (C), 61.3 (2×CH₂), 54.7 (CH₂), 49.7 (CH₂), 33.0 (CH₂), 31.4 (CH₂), 28.9 (CH₂), 28.0 (CH₂), 22.5 (CH₂), 14.3 (2×CH₃), 14.0 (CH₃). IR (film): 3028w, 2958m, 2928m, 2855w, 1730s, 1295w, 1455w, 1367w, 1249m, 1227m, 1138w, 1042m, 968w, 743w, 700w. MS (ESI+): 414.25 (75, [M+H]⁺), 436.23 (100, [M+Na]⁺), 849.44 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₃₆NO₄ ([M+H]⁺) 414.2639, found 414.2641.

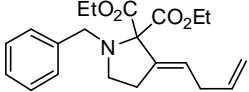
(*E*)-Diethyl 1-benzyl-3-(3-phenylprop-2-ynylidene)pyrrolidine-2,2-dicarboxylate **5i**



Pd(dppf)Cl₂ (10 mg, 12.5 µmol, 2.5 mol%) and CuI (5 mg, 25 µmol, 5.0 mol%) were suspended in THF (1 mL) and (iodoethynyl)benzene (192 mg, 89% pure, 0.75 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (159 mg, 0.5 mmol, 1.0 eq.) in THF (1 mL) was treated dropwise with NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (PE/Et₂O 7:1) afforded (*E*)-diethyl 1-benzyl-3-(3-phenylprop-2-ynylidene)pyrrolidine-2,2-dicarboxylate **5i** (117.0 mg, 0.28 mmol, 56%) as a clear oil.

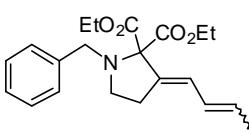
¹H-NMR (400 MHz, CDCl₃): 7.46-7.44 (*m*, 4H, H_{ar}), 7.37-7.26 (*m*, 6H, H_{ar}), 6.15 (*t*, 1H, J = 2.5 Hz, H_{olef}), 4.35 (*dq*, 2H, J = 10.8, 7.1 Hz, OCH₂), 4.30 (*dq*, 2H, J = 10.8, 7.1 Hz, OCH₂), 3.95 (*s*, 2H, CH₂Ph), 2.96-2.93 (*m*, 2H, CH₂N), 2.87-2.82 (*m*, 2H, CH₂C=C), 1.36 (*t*, 6H, J = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.4 (2×CO), 152.2 (C_{olef}), 139.3 (C_{ar}), 131.4 (2×CH_{ar}), 128.5 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.0 (CH_{ar}), 123.4 (C_{ar}), 106.3 (CH_{olef}), 95.6 (C_{sp}), 86.5 (C_{sp}), 77.8 (C), 61.7 (2×CH₂), 54.7 (CH₂), 49.3 (CH₂), 30.6 (CH₂), 14.3 (2×CH₃). IR (film): 3062w, 3030w, 2980m, 2936w, 2904w, 2833m, 1729s, 1492w, 1454w, 1443w, 1388w, 1367w, 1336s, 1249s, 1137m, 1040m, 860w, 757m, 691m. MS (ESI+): 418.20 (100, [M+H]⁺), 440.20 (43, [M+Na]⁺), 857.40 (72, [2M+Na]⁺). HRMS (ESI): calculated for C₂₆H₂₈NO₄ ([M+H]⁺) 418.2013, found 418.2013.

(E)-Diethyl 1-benzyl-3-(but-3-enylidene)pyrrolidine-2,2-dicarboxylate 5j

 Pd(dppf)Cl₂ (20 mg, 25 µmol, 2.5 mol%) and CuI (10 mg, 50 µmol, 5.0 mol%) were suspended in THF (2 mL) and allyl bromide (130 µL, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM) afforded (E)-diethyl 1-benzyl-3-(but-3-enylidene)pyrrolidine-2,2-dicarboxylate **5j** (260.6 mg, 0.73 mmol, 73%) as a clear yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.41-7.24 (*m*, 5H, H_{ar}), 5.86-5.76 (*m*, 2H, H_{olef}), 5.06 (*dq*, 1H, *J* = 17.1, 1.8 Hz, H_{olef}), 4.98 (*dq*, 1H, *J* = 10.1, 1.6 Hz, H_{olef}), 4.31 (*dq*, 2H, *J* = 10.7, 7.2 Hz, OCH₂), 4.26 (*dq*, 2H, *J* = 10.7, 7.2 Hz, OCH₂), 3.88 (*s*, 2H, CH₂Ph), 2.86 (*t*, 2H, *J* = 6.7 Hz, NCH₂), 2.83-2.78 (*m*, 2H, C=C-CH₂-C=C), 2.51-2.48 (*m*, 2H, NCH₂CH₂), 1.31 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.2 (2×CO), 139.5 (C_{olef}), 139.2 (C_{ar}), 135.6 (CH_{olef}), 128.5 (2×CH_{ar}), 128.2 (2×CH_{ar}), 126.9 (CH_{ar}), 123.4 (CH_{olef}), 115.1 (CH_{2olef}), 77.6 (C), 61.3 (2×CH₂), 54.8 (CH₂), 49.5 (CH₂), 33.3 (CH₂), 27.5 (CH₂), 14.3 (2×CH₃). IR (film): 2980m, 2833w, 1729s, 1495w, 1454w, 1367w, 1250s, 1228s, 1139m, 1043m, 912w, 743w, 699w. MS (ESI+): 358.3 (100, [M+H]⁺), 737.3 (85, [2M+Na]⁺). HRMS (ESI): calculated for C₂₁H₂₈NO₄ ([M+H]⁺) 358.2013, found 358.2011.

(E)-Diethyl 1-benzyl-3-((E/Z)-but-2-enylidene)pyrrolidine-2,2-dicarboxylate 5k

 Pd(dppf)Cl₂ (20 mg, 25 µmol, 2.5 mol%) and CuI (10 mg, 50 µmol, 5.0 mol%) were suspended in THF (2 mL) and (E/Z)-1-bromopropene (130 µL, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(benzyl(but-3-ynyl)amino)malonate **4** (317 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with LiHMDS (1.0 mL, 1 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 20 h at RT. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM) afforded (3E/Z)-diethyl 1-benzyl-3-(but-2-enylidene)pyrrolidine-2,2-dicarboxylate **5k** (71.8 mg, E/Z 5:1, 0.20 mmol, 20%) as a clear yellow oil.

¹H-NMR (400 MHz, CDCl₃): 7.42-7.17 (*m*, 5H, H_{ar}), 6.73-6.68 (*m*, 0.16H, C=CHCH=CHCH₃), 6.35 (*dt*, 0.84H, *J* = 10.8, 2.4 Hz, C=CHCH=CHCH₃), 6.12 (*ddq*, 0.84H, *J* = 14.9, 10.8, 1.5 Hz, C=CHCH=CHCH₃), 6.11-6.04 (*m*, 0.16H, C=CHCH=CHCH₃), 5.74 (*dq*, 0.84H, *J* = 14.9, 6.7 Hz, C=CHCH=CHCH₃), 5.62 (*dq*, 0.16H, *J* = 10.8, 7.0 Hz, C=CHCH=CHCH₃), 4.39-4.19 (*m*, 4H, 2×CH₂O), 3.92 (*s*, 2H, CH₂Ph), 2.96 (*t*, 0.32H, *J* = 6.7 Hz, NCH₂CH₂), 2.89 (*t*, 1.68H, *J* = 6.7 Hz, NCH₂CH₂), 2.62 (*bt*, 2H, *J* = 6.7 Hz, NCH₂CH₂), 1.80-1.76 (*m*, 3H, CH₃), 1.33 (*t*, 0.96H, *J* = 7.1 Hz, 2×CH₃), 1.31 (*t*, 5.04H, *J* = 7.1 Hz, 2×CH₃). Only the ¹³C-NMR data of the main isomer (*E*) is given: ¹³C-NMR (100 MHz, CDCl₃): 169.2 (2×CO), 139.6 (C_{olef}), 137.0 (C_{ar}), 130.9 (CH_{olef}), 128.5 (2×CH_{ar}), 128.3 (CH_{olef}), 128.2 (2×CH_{ar}), 126.9 (CH_{ar}), 125.3 (CH_{olef}), 77.7 (C), 61.3 (2×CH₂), 54.7 (CH₂), 49.7 (CH₂), 28.0 (CH₂), 18.4 (CH₃), 14.3 (2×CH₃).

(E)-Di-*tert*-butyl 1-benzyl-3-benzylidenepyrrolidine-2,2-dicarboxylate 8a

Pd(dppf)Cl₂ (20 mg, 25 µmol, 2.5 mol%) and CuI (10 mg, 50 µmol, 5.0 mol%) were suspended in THF (2 mL) and phenyl iodide (170 µL, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of di-*tert*-butyl 2-(benzyl(3-ynyl)amino)malonate **7a** (374 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with NaHMDS (1.66 mL, 0.6 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (PE/Et₂O 15:1, R_f (PE/Et₂O 5:1) = 0.47) afforded a mixture (32.4:1.0, 337.3 mg) of (*E*)-di-*tert*-butyl 1-benzyl-3-benzylidenepyrrolidine-2,2-dicarboxylate **8a** (0.73 mmol, 73%) and di-*tert*-butyl 1-benzyl-3-methylenepyrrolidine-2,2-dicarboxylate **9a** (0.02 mmol, 2%) as a clear oil.

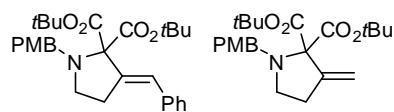
¹H-NMR (400 MHz, CDCl₃): 7.52-7.50 (*m*, 2H, H_{ar}), 7.39-7.35 (*m*, 6H, H_{ar}), 7.30-7.24 (*m*, 2H, H_{ar}), 6.87 (*t*, 1H, J = 2.4 Hz, C=CH), 4.14 (*s*, 2H, CH₂Ph), 3.00-2.97 (*m*, 2H, CH₂N), 2.87-2.83 (*m*, 2H, CH₂C=C), 1.59 (*s*, 18H, 2×C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (2×CO), 140.5 (C_{ar}), 140.2 (C_{ar}), 137.5 (C_{olef}), 128.6 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.2 (2×CH_{ar}), 126.9 (CH_{ar}), 126.8 (CH_{ar}), 125.9 (CH_{olef}), 82.1 (2×C), 79.5 (C), 54.7 (CH₂), 50.5 (CH₂), 30.2 (CH₂), 28.2 (6×(CH₃)). IR (film): 2976m, 2931w, 2832w, 1725s, 1494w, 1476w, 1454w, 2392w, 1368s, 1275m, 1255s, 1147s, 1024w, 983w, 841w, 736w, 697m. MS (ESI+): 450.21 (100, [M+H]⁺), 921.49 (76, [2M+Na]⁺). HRMS (ESI): calculated for C₂₈H₃₆NO₄ ([M+H]⁺) 450.2639, found 450.2626.

(E)-Diethyl 3-benzylidene-1-methylpyrrolidine-2,2-dicarboxylate 8b

Pd(dppf)Cl₂ (20 mg, 25 µmol, 2.5 mol%) and CuI (10 mg, 50 µmol, 5.0 mol%) were suspended in THF (2 mL) and phenyl iodide (170 µL, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of diethyl 2-(but-3-ynyl(methyl)amino)malonate **7b** (241 mg, 1.0 mmol, 1.0 eq.) in THF (1 mL) was treated dropwise with NaHMDS (1.66 mL, 0.6 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts *via* syringe (>98% transfer). The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (PE/EtOAc 3:2, R_f (PE/ Et₂O 1:1) = 0.22) afforded a mixture (9:1, 226.2 mg) of (*E*)-diethyl 3-benzylidene-1-methylpyrrolidine-2,2-dicarboxylate **8b** (0.66 mmol, 66%) and diethyl 1-methyl-3-methylenepyrrolidine-2,2-dicarboxylate **9b** as a clear oil.

¹H-NMR (400 MHz, CDCl₃): 7.37-7.32 (*m*, 4H, H_{ar}), 7.26-7.21 (*m*, 1H, H_{ar}), 6.77 (*t*, 1H, J = 2.5 Hz, CH_{olef}), 4.36-4.22 (*m*, 4H, 2×CH₂), 3.07 (*t*, 2H, J = 6.5 Hz, CH₂N), 2.88 (*dt*, 2H, J = 6.4, 2.5 Hz, CH₂C), 2.57 (*s*, 3H, CH₃), 1.31 (*t*, 6H, J = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.6 (CO), 139.9 (C_{olef}), 137.1 (C_{ar}), 128.6 (2×CH_{ar}), 128.3 (2×CH_{ar}), 127.0 (CH_{ar}), 125.9 (CH_{olef}), 78.7 (C), 61.5 (2×CH₂), 53.6 (CH₂), 36.7 (CH₃), 30.2 (CH₂), 14.3 (2×CH₃). IR (film): 2980w, 2937w, 2837w, 1727s, 1447w, 1247m, 1219s, 1172w, 1063m, 1036m, 763w, 695w, 510w. MS (ESI+): 318.14 (96, [M+H]⁺), 657.25 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₁₈H₂₄NO₄ ([M+H]⁺) 318.1700, found 318.1706.

(E)-Di-*tert*-butyl 3-benzylidene-1-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate 8c and di-*tert*-butyl 1-(4-methoxybenzyl)-3-methylenepyrrolidine-2,2-dicarboxylate 9c



Pd(dppf)Cl₂ (20 mg, 25 μmol, 2.5 mol%) and CuI (10 mg, 50 μmol, 5.0 mol%) were suspended in THF (2 mL) and phenyl iodide (170 μL, 1.5 mmol, 1.5 eq.) was added. In a separate flask a solution of di-*tert*-butyl 2-(but-3-enyl(4-methoxybenzyl)amino)malonate (404 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was treated dropwise with NaHMDS (1.66 mL, 0.6 M in toluene, 1.0 mmol, 1.0 eq.). After 5 min at RT the enolate solution was added over 5 min to the catalysts. The reaction immediately became warm and was stirred for 5 min at RT, after which TLC showed complete conversion. The reaction was filtered over silica (eluent: Et₂O) and the solvent evaporated. Purification by FC (DCM, R_f (DCM) = 0.61) afforded a mixture of (*E*)-di-*tert*-butyl 3-benzylidene-1-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate **8c** and di-*tert*-butyl 1-(4-methoxybenzyl)-3-methylenepyrrolidine-2,2-dicarboxylate **9c** (3.0 : 1.0, 394.7 mg, 0.64 mmol / 0.21 mmol, 64% / 21%) as a yellow oil. The main product could be obtained pure in a somewhat lower yield (58%). An analytical sample of the side product was obtained by preparative HPLC.

(E)-di-*tert*-butyl 3-benzylidene-1-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate 8c: White crystalline solid; mp 112.5 °C; ¹H-NMR (400 MHz, CDCl₃): 7.37 (d, 2H, J = 8.5 Hz, H_{ar}), 7.35-7.31 (m, 4H, H_{ar}), 7.25-7.20 (m, 1H, H_{ar}), 6.87 (d, 2H, J = 8.5 Hz, H_{ar}), 6.80 (t, 1H, J = 2.4 Hz, CH_{olef}), 3.99 (s, 2H, CH₂Ar), 3.81 (s, 3H, OCH₃), 2.90 (t, 2H, J = 6.5 Hz, CH₂N), 2.81-2.77 (m, 2H, CH₂C=C), 1.54 (s, 18H, C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃): 168.3 (2×CO), 158.6 (C_{ar}), 140.7 (C_{ar}), 137.5 (C_{olef}), 132.2 (C_{ar}), 129.5 (2×CH_{ar}), 128.6 (2×CH_{ar}), 128.3 (2×CH_{ar}), 126.9 (CH_{ar}), 125.7 (CH_{olef}), 113.6 (2×CH_{ar}), 82.1 (2×C), 79.4 (C), 55.3 (CH₃), 54.1 (CH₂), 50.2 (CH₂), 30.1 (CH₂), 28.2 (6×CH₃). IR (film): 2975s, 2932m, 2834m, 1724s, 1612m, 1511s, 1455m, 1329m, 1368s, 1299w, 1246s, 1105s, 1037m, 984m, 915m, 815s, 772m, 734m, 695m, 554w, 515m. MS (ESI+): 481.25 (77, [M+2H]⁺), 502.26 (57, [M+Na]⁺), 981.44 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₉H₃₇NNaO₅ ([M+Na]⁺) 502.2564, found 502.2567.

di-*tert*-butyl 1-(4-methoxybenzyl)-3-methylenepyrrolidine-2,2-dicarboxylate 9c:

¹H-NMR (400 MHz, CDCl₃): 7.35 (d, 2H, J = 8.5 Hz, H_{ar}), 6.85 (d, 2H, J = 8.5 Hz, H_{ar}), 5.39 (t, 1H, J = 2.2 Hz, CH_{olef}), 5.21 (t, 1H, J = 2.2 Hz, CH_{olef}), 3.93 (s, 2H, CH₂Ar), 3.80 (s, 3H, OCH₃), 2.81 (t, 2H, J = 6.4 Hz, CH₂N), 2.55 (t, 2H, J = 6.4 Hz, CH₂C=C), 1.51 (s, 18H, C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃): 168.0 (CO), 158.5 (C_{ar}), 147.7 (CH_{olef}), 129.5 (C_{ar}), 113.5 (4×CH_{ar}), 110.5 (C_{olef}), 81.9 (C), 78.1 (2×C), 55.2 (CH₃), 54.1 (CH₂), 49.5 (CH₂), 31.1 (CH₂), 28.0 (6×CH₃). IR (film): 2977m, 2933w, 2835w, 1725s, 1612w, 1512s, 1457w, 1393w, 1368m, 1283w, 1248s, 1150s, 1034m, 985w, 901w, 839m. MS (ESI+): 404.23 (100, [M+H]⁺), 426.21 (70, [M+Na]⁺). HRMS (ESI): calculated for C₂₃H₃₃NNaO₅ ([M+Na]⁺) 426.2251, found 426.2239.

(E)-2,2-Diethyl 1-methyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8d

To a solution of diethyl 2-(but-3-enyl(methoxycarbonyl)amino)malonate **7d** (142 mg, 0.5 mmol, 1.0 eq.) in THF (1 mL) was added dropwise NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The enolate solution was then added to a solution of Pd(dppf)Cl₂ (10 mg, 2.5 mol%), CuI (5 mg, 5.0 mol%) and phenyl iodide (85 μL,

0.75 mmol, 1.5 eq.) in THF (1 mL) *via* syringe (>98% transfer). After stirring for 5 min at room temperature the reaction mixture was filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. After purification by FC (PE/Et₂O 1:1, R_f (PE/Et₂O 1:1) = 0.13) (*E*-2,2-diethyl 1-methyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate **8d** (130.5 mg, 0.36 mmol, 72%) was obtained as a clear oil, together with 2,2-diethyl 1-methyl 3-methylenepyrrolidine-1,2,2-tricarboxylate **9d** (10.0:1.0). An analytical sample was obtained by preparative HPLC.

(E)-2,2-diethyl 1-methyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8d:

Mixture of rotamers: ¹H-NMR (400 MHz, CDCl₃): 7.38-7.26 (*m*, 5H, H_{ar}), 6.91-6.87 (*m*, 1H, H_{olef}), 4.35-4.18 (*m*, 4H, 2×CH₂O), 3.83-3.71 (*m*, 2H, CH₂N), 3.77/3.69 (*s*, 3H, CH₃), 2.99 (*dq*, 2H, *J* = 7.0, 2.4 Hz, CH₂C=C), 1.31-1.25 (*m*, 6H, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 167.0 (2×CO), 155.2/154.8 (CO), 138.3/137.5 (C_{olef}), 136.1/136.0 (C_{ar}), 128.7 (2×CH_{ar}), 128.5 (2×CH_{ar}), 127.7/127.6 (CH_{ar}), 126.2/126.2 (CH_{olef}), 74.7/73.7 (C), 62.2/62.1 (2×CH₂), 52.9/52.7 (CH₃), 46.9/46.3 (CH₂), 29.7/28.7 (CH₂), 14.0/14.0 (2×CH₃). IR (film): 2983m, 2958w, 2897wm 1749s, 1714s, 1448s, 1382s, 1231s, 1059m, 1042m, 773w, 696w. MS (ESI+): 362.17 (26, [M+H]⁺), 384.13 (81, [M+Na]⁺), 420.21 (44), 464.26 (98), 745.21 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₁₉H₂₃NNaO₆ ([M+Na]⁺) 384.1418, found 384.1417.

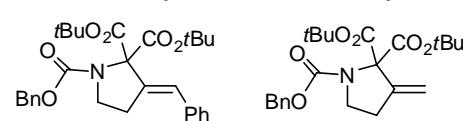
(E)-1-Benzyl 2,2-diethyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8e

To a solution of 1-benzyl 2,2-diethyl 3-methylenepyrrolidine-1,2,2-tricarboxylate **7e** (181 mg, 0.5 mmol, 1.0 eq.) THF (1 mL) was added dropwise NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The enolate solution was then added to a solution of Pd(dppf)Cl₂ (10 mg, 2.5 mol%), CuI (5 mg, 5.0 mol%) and phenyl iodide (85 μL, 0.75 mmol, 1.5 eq.) in THF (1 mL) *via* syringe (>98% transfer). After stirring for 5 min at room temperature the reaction mixture was filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. After purification by FC (PE/Et₂O 3:2, R_f (PE/Et₂O 2:1) = 0.26) (*E*-1-benzyl 2,2-diethyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate **8e** (169.8 mg, 0.36 mmol, 72%) was obtained as a clear oil, together with (*E*-1-benzyl 2,2-diethyl 3-methylenepyrrolidine-1,2,2-tricarboxylate **9e** (10.8 : 1.0). An analytical sample was obtained by preparative HPLC.

Mixture of rotamers: ¹H-NMR (400 MHz, CDCl₃): 7.41-7.26 (*m*, 10H, H_{ar}), 6.91 (*t*, 0.44H, *J* = 2.2 Hz, H_{olef}), 6.86 (*t*, 0.56H, *J* = 2.2 Hz, H_{olef}), 5.20 (*s*, 0.88H, CH₂Ar), 5.14 (*s*, 1.12H, CH₂Ar), 4.32-4.20 (*m*, 1.76H, 2×CH₂), 4.15-4.01 (*m*, 2.24H, 2×CH₂), 3.83 (*t*, 1.12H, *J* = 7.3 Hz, CH₂N), 3.80 (*t*, 0.88H, *J* = 7.2 Hz, CH₂N), 3.03-2.97 (*m*, 2H, CH₂C=C), 1.24 (*t*, 2.64H, *J* = 7.1 Hz, 2×CH₃), 1.12 (*t*, 3.36H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (125 MHz, CDCl₃): 167.0/166.9 (CO), 154.6/154.1 (CO), 138.4/137.3 (C_{olef}), 136.6/136.1 (C_{ar}), 136.1/136.0 (C_{ar}), 128.7/128.5 (2×CH_{ar}), 128.4/128.4 (CH_{ar}), 128.1/128.0 (CH_{ar}), 128.0/127.9 (CH_{ar}), 127.7/127.6 (CH_{ar}), 126.2/126.1 (CH_{olef}), 74.7/73.7 (C), 67.3/67.3 (CH₂), 62.2/62.1 (2×CH₂), 46.9/46.3 (CH₂), 29.7/28.7 (CH₂), 14.0/13.9 (2×CH₃). IR (film): 3032m, 1770w, 1748m, 1713s, 1410s, 1354m, 1230s, 1058m, 1041w, 771w, 696m. MS (ESI+): 460.17 (78, [M+Na]⁺), 496.26 (43), 540.30 (100), 897.31 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₂₇NNaO₆ ([M+Na]⁺) 460.1731, found 460.1731.

(E)-1-Benzyl 2,2-di-*tert*-butyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8f and 1-benzyl 2,2-di-*tert*-butyl 3-methylenepyrrolidine-1,2,2-tricarboxylate 9f

To a solution of di-*tert*-butyl 2-((benzyloxycarbonyl)-(but-3-



ynyl)amino)malonate **7f** (181 mg, 0.5 mmol, 1.0 eq.) in THF (1 mL) was added dropwise NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The enolate solution was then added to a solution of Pd(dppf)Cl₂ (10 mg, 2.5 mol%), CuI (5 mg, 5.0 mol%) and phenyl iodide (85 µL, 0.75 mmol, 1.5 eq.) in THF (1 mL). After stirring for 15 min at room temperature the reaction mixture was filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. After purification by FC (PE/Et₂O 4:1) a mixture of (*E*)-1-benzyl 2,2-diethyl 3-benzylideneprrolidine-1,2,2-tricarboxylate **8f** (0.21 mmol, 42%) and 1-benzyl 2,2-di-*tert*-butyl 3-methylenepyrrolidine-1,2,2-tricarboxylate **9f** (0.08 mmol, 16%) was obtained as a clear oil (3.2 : 1.0, 145.5 mg). Analytical samples were obtained by preparative HPLC.

(*E*)-1-benzyl 2,2-di-*tert*-butyl 3-benzylideneprrolidine-1,2,2-tricarboxylate **8f**:

Mixture of rotamers: ¹H-NMR (500 MHz, CDCl₃): 7.41-7.26 (*m*, 10H, H_{ar}), 6.88-6.85 (*m*, 1H, H_{olef}), 5.20 (*s*, 0.8H, CH₂Ph), 5.16 (*s*, 1.2H, CH₂Ph), 3.77 (*t*, 1.2H, *J* = 7.3 Hz, CH₂N), 3.73 (*t*, 0.8H, *J* = 7.2 Hz, CH₂N), 2.94 (*dt*, 2H, *J* = 7.2, 2.3 Hz, CH₂C=C), 1.45 (*s*, 7.2H, C(CH₃)₃), 1.36 (*s*, 10.8H, C(CH₃)₃). ¹³C-NMR (125 MHz, CDCl₃): 165.8 (CO), 154.5/154.4 (CO), 139.5/138.4 (C_{ar}), 136.8/136.6 (C_{olef}), 136.4/136.0 (C_{ar}), 128.6 (2×CH_{ar}), 128.5/128.4 (2×CH_{ar}), 128.4/128.3 (2×CH_{ar}), 128.0 (2×CH_{ar}), 127.9/127.8 (CH_{ar}), 127.5/127.4 (CH_{ar}), 125.6/125.4 (CH_{olef}), 82.2 (2×C), 75.6/74.6 (C), 67.4/67.0 (CH₂), 46.9/46.3 (CH₂), 29.5/28.7 (CH₂), 27.8/27.6 (6×CH₃). IR (film): 2976m, 2930w, 1715s, 1449w, 1411m, 1367m, 1353m, 1249m, 1152s, 1058w, 1023m, 844w, 803w, 769w, 736w, 696m. MS (ESI+): 516.22 (62, [M+Na]⁺), 595.28 (100). HRMS (ESI): calculated for C₂₉H₃₅NNaO₆ ([M+Na]⁺) 516.2357, found 516.2342.

1-benzyl 2,2-di-*tert*-butyl 3-methylenepyrrolidine-1,2,2-tricarboxylate **9f**:

Mixture of rotamers: ¹H-NMR (500 MHz, CDCl₃): 7.40-7.26 (*m*, 5H, H_{ar}), 5.45-5.43 (*m*, 1H, H_{olef}), 5.18 (*s*, 0.8H, CH₂Ph), 5.17-5.15 (*m*, 1H, H_{olef}), 5.13 (*s*, 1.2H, CH₂Ph), 3.70 (*t*, 1.2H, *J* = 7.3 Hz, CH₂N), 3.64 (*t*, 0.8H, *J* = 7.3 Hz, CH₂N), 2.69-2.66 (*m*, 2H, CH₂C=C), 1.44 (*s*, 7.2H, C(CH₃)₃), 1.34 (*s*, 10.8H, C(CH₃)₃). ¹³C-NMR (125 MHz, CDCl₃): 165.7/165.6 (2×CO), 154.5/154.3 (CO), 147.0/145.9 (C_{olef}), 136.8/136.0 (CH), 128.4/128.2 (2×CH_{ar}), 128.0/127.9 (2×CH_{ar}), 127.9/127.8 (CH_{ar}), 110.7/110.6 (CH_{olef}), 82.1 (2×C), 74.7/73.9 (C), 67.3/67.0 (CH₂), 46.3/45.9 (CH₂), 31.5/30.6 (CH₂), 27.7/27.5 (6×CH₃). IR (film): 2977m, 2932w, 1771m, 1715s, 1409m, 1367m, 1352m, 1250m, 1153s, 1063w, 1024m, 907w, 844w, 815w, 697w. MS (ESI+): 440.20 (64, [M+Na]⁺), 520.20 (100), 857.31 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₃H₃₁NNaO₆ ([M+Na]⁺) 440.2044, found 440.2043.

2. 2. Cyclization reactions for the synthesis of piperidines

(*E*)-Diethyl 1-benzyl-3-benzylideneperidine-2,2-dicarboxylate **11a**

To a solution of ethyl diethyl 2-(benzyl(pent-4-ynyl)amino)malonate **10** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and phenyl iodide (85 µL, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS sol. (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred 3 d at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 8:1, R_f (PE/Et₂O 2:1) = 0.5) gave (*E*)-diethyl 1-benzyl-3-benzylideneperidine-2,2-dicarboxylate **11a** (142 mg, 0.348 mmol, 70%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.52-7.51 (*m*, 2H, H_{ar}), 7.37-7.30 (*m*, 4H, H_{ar}), 7.27-7.22 (*m*, 4H, H_{ar}), 6.31 (*s*, 1H, H_{olef}), 4.34 (*q*, 4H, *J* = 7.1 Hz, 2×CH₂O), 3.95 (*s*, 2H, CH₂Ph), 2.70-2.65 (*m*, 2H, CH₂N), 2.50-2.47 (*m*, 2H, CH₂C=C), 1.60-1.53 (*m*, 2H, NCH₂CH₂CH₂), 1.33 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 170.3 (2×CO), 140.4 (C_{olef}), 137.2 (C_{ar}), 137.1 (C_{ar}), 129.1 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.1 (4×CH_{ar}), 126.8 (2×CH_{ar}), 126.5 (CH_{olef}), 80.7 (C), 61.6 (2×CH₂), 58.7 (CH₂), 47.0 (CH₂), 25.9 (CH₂), 25.3 (CH₂), 14.2 (2×CH₃). IR (film): 2979m, 2938w, 2852w, 2809w, 1729s, 1494w, 1446w, 1286m, 1245m, 1224m, 1073m, 1045m, 760w, 735w, 701m. MS (ESI+): 408.22 (36, [M+H]⁺), 430.20 (43, [M+Na]⁺), 837.41 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₂₉NNaO₄ ([M+Na]⁺) 430.1989, found 430.1990.

(E)-Diethyl 1-benzyl-3-(4-methoxybenzylidene)piperidine-2,2-dicarboxylate 11b

To a solution of ethyl diethyl 2-(benzyl(pent-4-ynyl)amino)malonate **10** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and 4-iodo anisole (176 mg, 0.75 mmol, 1.5 eq.) followed by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred for 3 d at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 6:1) gave (*E*)-diethyl 1-benzyl-3-(4-methoxybenzylidene)piperidine-2,2-dicarboxylate **11b** (92.6 mg, 0.21 mmol, 42%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.52 (*d*, 2H, *J* = 7.3 Hz, H_{ar}), 7.32 (*t*, 2H, *J* = 7.4 Hz, H_{ar}) 7.24 (*t*, 1H, *J* = 7.3 Hz, H_{ar}), 7.19 (*d*, 2H, *J* = 8.6 Hz, H_{ar}), 6.89 (*d*, 2H, *J* = 8.6 Hz, H_{ar}), 6.26 (*s*, 1H, H_{olef}), 4.34 (*q*, 4H, *J* = 7.1 Hz, 2×CH₂), 3.95 (*s*, 2H, CH₂Ph), 3.83 (*s*, 3H, OCH₃), 2.69-2.60 (*m*, 2H, CH₂N), 2.50 (*t*, 2H, *J* = 6.2 Hz, CH₂C=C), 1.57 (*qn*, 2H, *J* = 6.2, NCH₂CH₂CH₂), 1.33 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 170.4 (2×CO), 158.4 (C_{ar}), 140.4 (C_{olef}), 136.0 (C_{ar}), 130.3 (2×CH_{ar}), 129.6 (C_{ar}), 128.3 (2×CH_{ar}), 128.1 (2×CH_{ar}), 126.7 (CH_{ar}), 126.0 (CH_{olef}), 113.5 (2×CH_{ar}), 80.7 (C), 61.5 (2×CH₂), 58.7 (CH₂), 55.2 (CH₃), 46.9 (CH₂), 25.8 (CH₂), 25.2 (CH₂), 14.2 (2×CH₃). IR (film): 2979m, 2937m, 2837w, 1729s, 1607m, 1510s, 1445m, 1293s, 1143m, 1029s, 737w, 700w. MS (ESI+): 438.31 (75, [M+H]⁺), 460.20 (43, [M+Na]⁺), 897.38 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₆H₃₂NO₅ ([M+H]⁺) 438.2275, found 438.2277.

(E)-Diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzylidene)piperidine-2,2-dicarboxylate 11c

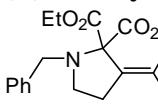
To a solution of ethyl diethyl 2-(benzyl(pent-4-ynyl)amino)malonate **10** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and methyl 4-iodo benzoate (197 mg, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred 3 d at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 3:1) gave (*E*)-diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzylidene)piperidine-2,2-dicarboxylate **11c** (129.9 mg, approx. 95% purity, 0.28 mmol, 56%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 8.02 (*d*, 2H, *J* = 8.3 Hz, H_{ar}), 7.51 (*d*, 2H, *J* = 7.3 Hz, H_{ar}), 7.34-7.29 (*m*, 4H, H_{ar}), 7.26-7.22 (*m*, 1H, H_{ar}), 6.33 (*s*, 1H, H_{olef}), 4.35 (*q*, 4H, *J* = 7.1 Hz, 2×CH₂), 3.96 (*s*, 2H, CH₂Ph), 3.92 (*s*, 3H, CO₂CH₃), 2.69-2.67 (*m*, 2H, CH₂N), 2.49 (*t*, 2H, *J* = 6.2 Hz, CH₂C=C), 1.58 (*qn*, 2H, *J* = 6.2 Hz, NCH₂CH₂CH₂),

1.34 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 170.1 (2×CO), 166.9 (CO), 142.0 (C_{ar}), 140.2 (C_{olef}), 138.9 (C_{ar}), 129.4 (2×CH_{ar}), 129.1 (2×CH_{ar}), 128.4 (C_{ar}), 128.3 (2×CH_{ar}), 128.1 (2×CH_{ar}), 126.8 (CH_{ar}), 125.6 (CH_{olef}), 80.6 (C), 61.6 (2×CH₂), 58.7 (CH₂), 52.1 (CH₃), 46.8 (CH₂), 26.0 (CH₂), 25.2 (CH₂), 14.2 (2×CH₃). IR (film): 2980w, 2952w, 2853w, 1725s, 1606w, 1437m, 1279s, 1250m, 1112m, 1028m, 881w, 770w, 735w, 701w. MS (ESI+): 466.22 (91, [M+H]⁺), 488.20 (100, [M+Na]⁺), 953.41 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₇H₃₂NO₆ ([M+H]⁺) 466.2224, found 466.2225.

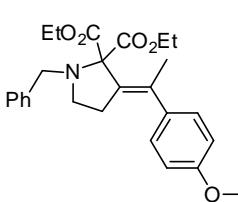
2. 3. Cyclization of internal alkynyl amino malonates

(*E*)-Diethyl 1-benzyl-3-(1-phenylethylidene)pyrrolidine-2,2-dicarboxylate 13a

 To a solution of diethyl 2-(benzyl(pent-3-ynyl)amino)malonate **12a** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and phenyl iodide (85 μL 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred for 3 h at room temperature, filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 5:1, R_f (PE/Et₂O 5:1) = 0.31) gave (*E*)-diethyl 1-benzyl-3-(1-phenylethylidene)pyrrolidine-2,2-dicarboxylate **13a** (180.3 mg, 0.44 mmol, 88%) as a white crystalline solid; mp 83–84 °C.

¹H-NMR (400 MHz, CDCl₃): 7.38–7.18 (*m*, 10H, H_{ar}), 4.36 (*dq*, 2H, *J* = 10.8, 7.2 Hz, OCH₂), 4.33 (*dq*, 2H, *J* = 10.8, 7.2 Hz, OCH₂), 3.96 (*s*, 2H, CH₂Ph), 2.79 (*t*, 2H, *J* = 6.6 Hz, CH₂N), 2.34 (*tq*, 2H, *J* = 6.6, 1.8 Hz, CH₂C=C), 2.03 (*t*, 3H, *J* = 1.8 Hz, CH₃C=C), 1.36 (*t*, 6H, *J* = 7.2 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.6 (2×CO), 144.6 (CH_{olef}), 139.7 (CH_{ar}), 135.3 (CH_{ar}), 134.6 (CH_{olef}), 128.4 (2×CH_{ar}), 128.2 (2×CH_{ar}), 128.2 (2×CH_{ar}), 127.4 (2×CH_{ar}), 126.9 (CH_{ar}), 126.6 (CH_{ar}), 77.2 (C), 61.3 (2×CH₂), 54.5 (CH₂), 50.3 (CH₂), 31.7 (CH₂), 22.4 (CH₃), 14.3 (2×CH₃). IR (film): 3060w, 3026w, 2980m, 2934w, 2835w, 1729s, 1600w, 1494m, 1444m, 1367w, 1252s, 1228s, 1138w, 1074w, 1046s, 1027w, 859w, 764m, 734m, 700s. MS (ESI+): 408.18 (100, [M+H]⁺), 430.20 (49, [M+Na]⁺), 509.32 (81), 837.31 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₂₉NNaO₄ ([M+Na]⁺) 430.1994, found 430.1982.

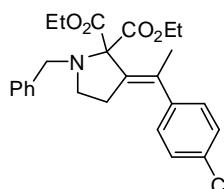
(*E*)-Diethyl 1-benzyl-3-(1-(4-methoxyphenyl)ethylidene)pyrrolidine-2,2-dicarboxylate 13b

 To a solution of ethyl 2-(benzyl(pent-3-ynyl)amino)propanoate **12a** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and 4-iodoanisole (176 mg, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred for 15 h at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 3:1) gave (*E*)-diethyl 1-benzyl-3-(1-(4-methoxyphenyl)ethylidene)pyrrolidine-2,2-dicarboxylate **13b** (178.5 mg, 0.41 mmol, 82%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.39–7.37 (*m*, 2H, H_{ar}), 7.33–7.29 (*m*, 2H, H_{ar}), 7.26–7.22 (*m*, 1H, H_{ar}), 7.15–7.12 (*m*, 2H, H_{ar}), 6.89–6.86 (*m*, 2H, H_{ar}), 4.41–4.29 (*m*, 4H, 2×CH₂O), 3.97 (*s*, 2H, CH₂Ph), 3.81 (*s*, 3H, OCH₃), 2.80 (*t*, 2H, *J* = 6.5 Hz, CH₂N), 2.40 (*tq*, 2H, *J* = 6.5, 1.8 Hz, CH₂C=C), 2.03 (*t*, 3H, *J* = 1.8 Hz, CH₃), 1.37 (*t*, 6H, *J* =

7.1 Hz, 2 \times CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.7 (2 \times CO), 158.2 (C_{ar}), 139.6 (C_{ar}), 137.0 (C_{ar}), 135.0 (C_{olef}), 134.1 (C_{olef}), 128.5 (2 \times CH_{ar}), 128.4 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 126.9 (CH_{ar}), 113.5 (2 \times CH_{ar}), 77.2 (C), 61.3 (2 \times CH₂), 55.2 (OCH₃), 54.5 (CH₂), 50.3 (CH₂), 31.8 (CH₂), 22.4 (CH₃), 14.3 (2 \times CH₃). IR (film): 3029w, 2980m, 2935w, 2836m, 1729s, 1608m, 1510s, 1455m, 1367w, 1246s, 1178m, 1139w, 1075w, 1045s, 834m, 733w, 700w. MS (ESI+): 438.20 (80, [M+H]⁺), 460.18 (77, [M+Na]⁺), 897.35 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₆H₃₁NNaO₅ ([M+Na]⁺) 460.2094, found 460.2085.

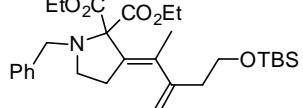
(E)-Diethyl 1-benzyl-3-(1-(4-(methoxycarbonyl)phenyl)ethylidene)pyrrolidine-2,2-dicarboxylate 13c



To a solution of diethyl 2-(benzyl(pent-3-ynyl)amino)propanoate **12a** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and methyl 4-iodobenzoate (197 mg, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 0.37 mmol, 1.0 eq.). The reaction was stirred for 3 d at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 4:1) gave (E)-diethyl 1-benzyl-3-(1-(4-(methoxycarbonyl)phenyl)ethylidene)pyrrolidine-2,2-dicarboxylate **13c** (174.7 mg, 0.37 mmol, 75%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 8.02-8.00 (m, 2H, CH_{ar}), 7.37-7.35 (m, 2H, H_{ar}), 7.32-7.22 (m, 5H, H_{ar}), 4.41-4.29 (m, 4H, 2 \times CH₂O), 3.96 (s, 2H, CH₂Ph), 3.92 (s, 3H, CO₂CH₃), 2.79 (t, 2H, J = 6.6 Hz, NCH₂), 2.34 (tq, 2H, J = 6.6, 1.8 Hz, CH₂C=C), 2.04 (t, 3H, J = 1.8 Hz, C=CCH₃), 1.37 (t, 6H, J = 7.1 Hz, 2 \times CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.4 (2 \times CO), 166.9 (CO), 149.4 (C_{ar}), 139.5 (C_{ar}), 136.3 (C_{ar}), 133.8 (C_{olef}), 129.7 (2 \times CH_{ar}), 128.5 (C_{olef}), 128.3 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 127.5 (2 \times CH_{ar}), 126.9 (CH_{ar}), 77.2 (C), 61.4 (2 \times CH₂), 54.4 (CH₂), 52.0 (CH₃), 50.3 (CH₂), 31.7 (CH₂), 22.0 (CH₃), 14.3 (2 \times CH₃). IR (film): 2980w, 2840w, 1724s, 1607w, 1436w, 1278s, 1253m, 1229m, 1113w, 1048w, 1019w, 860w, 777w, 711w, 700w. MS (ESI+): 466.20 (75, [M+H]⁺), 488.18 (100, [M+Na]⁺), 953.37 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₇H₃₁NNaO₆ ([M+Na]⁺) 488.2044, found 488.2043.

(E)-Diethyl 1-benzyl-3-(5-(tert-butyldimethylsilyloxy)-3-methylenepentan-2-ylidene)pyrrolidine-2,2-dicarboxylate 13d



To a solution of diethyl 2-(benzyl(pent-3-ynyl)amino)malonate **12a** (166 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and *tert*-butyl(3-iodobut-3-enyloxy)dimethylsilane (234 mg, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS sol. (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred for 15 h at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 8:1) gave (E)-diethyl 1-benzyl-3-(5-(tert-butyldimethylsilyloxy)-3-methylenepentan-2-ylidene)pyrrolidine-2,2-dicarboxylate **13d** (94.7 mg, 0.18 mmol, 37%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.37-7.35 (m, 2H, H_{ar}), 7.32-7.28 (m, 2H, H_{ar}), 7.25-7.21 (m, 1H, H_{ar}), 4.96-4.94 (m, 1H, H_{olef}), 4.81 (d, 1H, J = 2.2 Hz, H_{olef}), 4.34-4.21 (m, 4H, 2 \times CH₂O), 3.92 (s, 2H, CH₂Ph), 3.65 (t, 2H, J = 7.1 Hz, CH₂OTBS), 2.78 (t, 2H, J = 6.6 Hz, CH₂N), 2.53 (tq, 2H, J = 6.6, 1.8 Hz, NCH₂CH₂), 2.37 (t, 2H, J = 7.1 Hz, OCH₂CH₂), 1.77 (t, 3H, J = 1.8 Hz, C=CCH₃), 1.32 (t, 6H, J = 7.1 Hz, 2 \times OCH₂CH₃), 0.88 (s, 9H, C(CH₃)₃), 0.05 (s, 6H, Si(CH₃)₂). ¹³C-NMR (100 MHz,

CDCl_3): 169.6 (2 \times CO), 148.7 (C_{olef}), 139.7 (C_{olef}), 135.1 (C_{ar}), 134.4 (C_{olef}), 128.3 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 126.8 (CH_{ar}), 113.4 (CH_{2olef}), 76.8 (C), 61.2 (CH₂), 61.2 (2 \times CH₂), 54.4 (CH₂), 50.2 (CH₂), 38.6 (CH₂), 31.4 (C), 25.9 ((CH₃)₃), 19.7 (CH₃), 18.2 (CH₂), 14.3 (2 \times CH₃), -5.3 (Si(CH₃)₂). IR (film): 2955m, 2929m, 2856m, 1744s, 1730s, 1472w, 1455w, 1387w, 1364w, 1252s, 1226s, 1095s, 1046s, 836s, 775m, 684w. MS (ESI+): 516.31 (77, [M+H]⁺), 538.29 (100, [M+Na]⁺). HRMS (ESI): calculated for C₂₉H₄₅NNaO₅Si ([M+Na]⁺) 538.2959, found 538.2957.

(E)-Diethyl 1-benzyl-3-(1-phenylpentylidene)pyrrolidine-2,2-dicarboxylate 13e

To a solution of diethyl 2-(benzyl(oct-3-ynyl)amino)malonate **12b** (187 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and phenyl iodide (85 μ L, 0.75 mmol, 1.5 eq.) followed by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred 3 d at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 6:1) gave (E)-diethyl 1-benzyl-3-(1-phenylpentylidene)pyrrolidine-2,2-dicarboxylate **13e** (153.6 mg, 0.34 mmol, 68%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.36-7.21 (m, 8H, H_{ar}), 7.14-7.12 (m, 2H, H_{ar}), 4.38-4.28 (m, 4H, 2 \times OCH₂), 3.95 (s, 2H, CH₂Ph), 2.78 (t, 2H, J = 6.6 Hz, CH₂N), 2.40-2.38 (m, 2H, NCH₂CH₂), 2.29 (t, 2H, J = 6.6 Hz, CH₂nPr), 1.37 (t, 6H, J = 7.1 Hz, 2 \times CH₃), 1.26-1.10 (m, 4H, CH₃CH₂CH₂), 0.80 (t, 3H, J = 7.2 Hz, CH₃CH₂CH₂). ¹³C-NMR (100 MHz, CDCl₃): 169.7 (CO), 142.9 (C_{ar}), 139.7 (C_{olef}), 139.5 (C_{ar}), 134.7 (C_{olef}), 128.3 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 128.1 (2 \times CH_{ar}), 127.9 (2 \times CH_{ar}), 126.8 (CH_{ar}), 126.4 (CH_{ar}), 76.8 (C), 61.3 (2 \times CH₂), 54.3 (CH₂), 50.1 (CH₂), 35.3 (CH₂), 31.4 (CH₂), 29.5 (CH₂), 22.9 (CH₂), 14.3 (2 \times CH₃), 13.9 (CH₃). IR (film): 2959m, 2930m, 2871w, 1730s, 1494w, 1454w, 1227s, 1044m, 701m. MS (ESI+): 450.27 (56, [M+H]⁺), 472.25 (38, [M+Na]⁺), 921.45 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₈H₃₅NNaO₄ ([M+Na]⁺) 472.2458, found 472.2452.

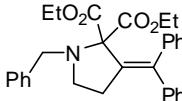
(E)-Diethyl 1-benzyl-3-(1-(4-(methoxycarbonyl)phenyl)pentylidene)pyrrolidine-2,2-dicarboxylate 13f

To a solution of diethyl 2-(benzyl(oct-3-ynyl)amino)malonate **12b** (187 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5 mol%) and methyl 4-iodo benzoate (197 mg, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS sol. (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred for 3 d at 60 °C, filtered through a plug of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 6:1) gave (E)-diethyl 1-benzyl-3-(1-(4-(methoxycarbonyl)phenyl)pentylidene)pyrrolidine-2,2-dicarboxylate **13f** (173.6 mg, 0.34 mmol, 68%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 8.02 (d, 2H, J = 8.1 Hz, H_{ar}), 7.37-7.34 (m, 2H, H_{ar}), 7.30 (t, 2H, J = 7.5 Hz, CH_{ar}), 7.23-7.21 (m, 1H, H_{ar}), 7.22 (d, 2H, J = 8.2 Hz, H_{ar}), 4.39-4.27 (m, 4H, 2 \times CH₂O), 3.96 (s, 2H, CH₂Ph), 3.91 (s, 3H, ArCO₂CH₃), 2.79 (t, 2H, J = 6.6 Hz, CH₂N), 2.44-2.40 (m, 2H, NCH₂CH₂), 2.27 (t, 2H, J = 6.6 Hz, C=CArCH₂), 1.37 (t, 6H, J = 7.1 Hz, 2 \times CH₃), 1.27-1.18 (m, 2H, CH₂CH₂CH₂CH₃), 1.14-1.06 (m, 2H, CH₂CH₂CH₂CH₃), 0.79 (t, 3H, J = 7.2 Hz, CH₂CH₂CH₂CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.5 (2 \times CO), 167.0 (CO), 147.9 (C_{ar}), 139.6 (C_{ar}), 138.8 (C_{ar}), 135.5 (C_{olef}), 129.6 (2 \times CH_{ar}), 128.4 (C_{olef}), 128.3 (2 \times CH_{ar}), 128.2 (2 \times CH_{ar}), 128.0 (2 \times CH_{ar}), 126.9 (CH_{ar}), 76.9 (C), 61.4 (2 \times CH₂), 54.3 (CH₂), 52.0 (CH₃), 50.0

(CH₂), 35.1 (CH₂), 31.4 (CH₂), 29.5 (CH₂), 22.9 (CH₂), 14.3 (2×CH₃), 13.9 (CH₃). IR (film): 2957w, 2931m, 2859w, 1724s, 1606w, 1435w, 1277s, 1252w, 1228w, 1113m, 1043m, 860w, 780w, 716w, 699w. MS (ESI+): 508.25 (100, [M+H]⁺), 530.25 (97, [M+Na]⁺), 546.24 (55, [M+K]⁺). HRMS (ESI): calculated for C₃₀H₃₈NO₆ ([M+H]⁺) 508.2694, found 508.2695.

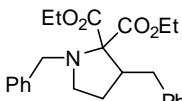
Diethyl 1-benzyl-3-(diphenylmethylenepyrrrolidine-2,2-dicarboxylate 13g

 To a solution of diethyl 2-(benzyl(4-phenylbut-3-enyl)amino)malonate **12c** (197 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 0.025 mmol, 5.0 mol%) and phenyl iodide (85 μL, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred at room temperature for 2.5 d, filtered through a pad of silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 10:1 to 5:1) afforded diethyl 1-benzyl-3-(diphenylmethylenepyrrrolidine-2,2-dicarboxylate **13g** (199.8 mg, 0.42 mmol, 83%) as a white solid; mp 101 °C.

¹H-NMR (400 MHz, CDCl₃): 7.37-7.17 (*m*, 15H, H_{ar}), 4.12 (*dq*, 2H, *J* = 10.8, 7.1 Hz, OCH₂), 3.96 (*dq*, 2H, *J* = 10.8, 7.1 Hz, OCH₂), 3.83 (*s*, 2H, CH₂Ph), 2.81 (*t*, 2H, *J* = 6.4 Hz, CH₂N), 2.61 (*t*, 2H, *J* = 6.4 Hz, CH₂C=C), 1.21 (*t*, 6H, *J* = 7.1 Hz, 2×CH₃). ¹³C-NMR (100 MHz, CDCl₃): 168.6 (2×CO), 143.2 (C), 140.9 (C), 139.4 (C), 138.3 (C), 138.0 (C), 129.2 (2×CH_{ar}), 128.5 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.2 (2×CH_{ar}), 128.2 (2×CH_{ar}), 127.8 (2×CH_{ar}), 126.9 (CH_{ar}), 126.9 (CH_{ar}), 126.7 (CH_{ar}), 77.2 (C), 61.1 (2×CH₂), 54.7 (CH₂), 49.5 (CH₂), 32.1 (CH₂), 14.1 (2×CH₃). IR (film): 3058w, 3027w, 2980m, 2834w, 1739s, 1599w, 1493m, 1443m, 1366w, 1225s, 1133w, 1074w, 1043s, 862w, 753m, 700s. MS (ESI+): 331.18 (42), 470.25 (19, [M+H]⁺), 492.23 (33, [M+Na]⁺), 679.37 (20), 961.46 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₃₀H₃₁NNaO₄ ([M+Na]⁺) 492.2145, found 492.2137.

2. 4. Cyclization of alkenyl amino malonates

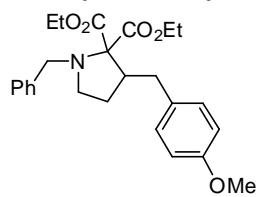
Diethyl 1,3-dibenzylpyrrolidine-2,2-dicarboxylate 15a

 To a solution of diethyl 2-(benzyl(but-3-enyl)amino)malonate **14** (160 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5.0 mol%) and phenyl iodide (85 μL, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS solution (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred at room temperature for 2.5 d, filtered through a pad of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 10:1) afforded diethyl 1,3-dibenzylpyrrolidine-2,2-dicarboxylate **15a** (138.5 mg, ca. 95% pure, 0.33 mmol, 67%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.41-7.39 (*m*, 2H, H_{ar}), 7.33-7.18 (*m*, 8H, H_{ar}), 4.38-4.22 (*m*, 4H, 2×CH₂O), 4.05 (*d*, 1H, *J* = 13.4 Hz, NCHHPh), 3.81 (*d*, 1H, *J* = 13.4 Hz, NCHHPh), 3.17 (*dd*, 1H, *J* = 13.0, 3.3 Hz, CHH), 3.06-2.98 (*m*, 1H, CHH), 2.86-2.75 (*m*, 2H, 2×CHH), 2.44 (*t*, 1H, *J* = 12.4 Hz, CHH), 1.83 (*ddt*, 1H, *J* = 12.6, 4.6, 8.3 Hz, CHH), 1.71 (*dddt*, 1H, *J* = 12.6, 9.6, 8.2, 6.6 Hz, CHH), 1.35 (*t*, 3H, *J* = 7.1 Hz, CH₃), 1.33 (*t*, 3H, *J* = 7.2 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.91 (CO), 169.4 (CO), 140.5 (C_{ar}), 140.1 (C_{ar}), 129.0 (2×CH_{ar}), 128.4 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.2 (2×CH_{ar}), 126.8 (CH_{ar}), 126.1 (CH_{ar}), 78.1 (C), 61.2 (CH₂), 61.0 (CH₂), 55.5 (CH₂), 50.7 (CH₂), 47.7 (CH₂), 37.5 (CH), 27.8 (CH₂), 14.5 (CH₃), 14.3 (CH₃). IR (film): 3085w, 3062w, 3027w, 2979m, 2937w, 1727s, 1495w, 1453w, 1367w,

1270m, 1202m, 1143m, 1074w, 1059w, 1030w, 745m, 699m. MS (ESI+): 396.23 (75, [M+H]⁺), 418.21 (62, [M+Na]⁺), 813.43 (100, [2M+Na]⁺). HRMS (ESI): calculated for C₂₄H₂₉NNaO₄ ([M+Na]⁺) 418.1989, found 418.1994.

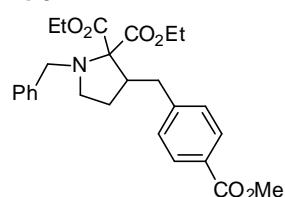
Diethyl 1-benzyl-3-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate 15b



To a solution of diethyl 2-(benzyl(but-3-enyl)amino)malonate **14** (160 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5.0 mol%) and 4-iodo anisole (176 mg 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS solution (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred at 60 °C for 15 h, filtered through a pad of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 6:1) afforded diethyl 1-benzyl-3-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate **15b** (140.3 mg, 0.33 mmol, 66%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.44 (*d*, 2H, *J* = 7.4 Hz, H_{ar}), 7.33 (*t*, 2H, *J* = 7.4 Hz, H_{ar}), 7.27-7.23 (*m*, 1H, H_{ar}), 7.15 (*d*, 2H, *J* = 8.5 Hz, H_{ar}), 6.85 (*d*, 2H, *J* = 8.5 Hz, H_{ar}), 4.40-4.27 (*m*, 4H, 2×CH₂O), 4.09 (*d*, 1H, *J* = 13.4 Hz, CHHPh), 3.86 (*d*, 1H, *J* = 13.4 Hz, CHHPh), 3.80 (*s*, 3H, OCH₃), 3.14 (*dd*, 1H, *J* = 13.1, 3.2 Hz, CHHAr), 3.02 (*ddd*, 1H, *J* = 12.0, 8.3, 3.2 Hz, CH), 2.90-2.80 (*m*, 2H, CH₂N), 2.42 (*dd*, 1H, *J* = 12.0, 13.1 Hz, CHHAr), 1.87 (*ddd*, 1H, *J* = 12.6, 8.3, 4.4 Hz, NCH₂CHH), 1.73 (*ddd*, 1H, *J* = 12.6, 9.4, 8.3, 6.6 Hz, NCH₂CHH), 1.38 (*t*, 3H, *J* = 7.2 Hz, OCH₂CH₃), 1.35 (*t*, 3H, *J* = 7.2 Hz, OCH₂CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.9 (CO), 169.4 (CO), 158.0 (C_{ar}), 140.2 (C_{ar}), 132.5 (C_{ar}), 129.8 (2×CH_{ar}), 128.3 (2×CH_{ar}), 128.2 (2×CH_{ar}), 126.8 (CH_{ar}), 113.8 (2×CH_{ar}), 78.1 (C), 61.2 (CH₂O), 60.9 (CH₂O), 55.5 (CH₂), 55.2 (CH₃), 50.7 (CH₂), 47.9 (CH), 36.6 (CH₂), 27.7 (CH₂), 14.4 (CH₃), 14.3 (CH₃). IR (film): 3062w, 3028w, 2979m, 2905w, 2835w, 1726s, 1611w, 1512s, 1454w, 1367w, 1246s, 1202w, 1143w, 1034s, 742w, 699w. MS (ESI+): 426.25 (84, [M+H]⁺), 448.23 (100, [M+Na]⁺), 464.21 (77, [M+K]⁺), 873.49 (84, [2M+Na]⁺). HRMS (ESI): calculated for C₂₅H₃₂NO₅ ([M+H]⁺) 426.2275, found 426.2274.

Diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzyl)pyrrolidine-2,2-dicarboxylate 15c



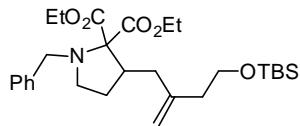
To a solution of diethyl 2-(benzyl(but-3-enyl)amino)malonate **14** (160 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5.0 mol%) and methyl 4-iodo benzoate (197 mg, 0.75 mmol, 1.5 eq.) followed by NaHMDS (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.) were added dropwise. The reaction was then stirred at 60 °C for 15 h.

Then the reaction mixture was filtered through a pad of silica (eluent: Et₂O) and the solvent was removed. Purification by FC (PE/Et₂O 3:1) afforded diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzyl)pyrrolidine-2,2-dicarboxylate **15c** (159.6 mg 0.35 mmol, 70%) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃): 7.96 (*d*, 2H, *J* = 8.2 Hz, H_{ar}), 7.40 (*d*, 2H, *J* = 7.4 Hz, H_{ar}), 7.32-7.21 (*m*, 5H, H_{ar}), 4.39-4.24 (*m*, 4H, 2×CH₂O), 4.08 (*d*, 1H, *J* = 13.3 Hz, CHHPh), 3.89 (*s*, 3H, CO₂CH₃), 3.80 (*d*, 1H, *J* = 13.3 Hz, CHHPh), 3.23 (*dd*, 1H, *J* = 13.1, 3.3 Hz, CHHAr), 3.04 (*ddd*, 1H, *J* = 11.7, 8.4, 3.3 Hz, CH), 2.87-2.77 (*m*, 2H, CH₂N), 2.52 (*dd*, 1H, *J* = 13.1, 11.7 Hz, CHHAr), 1.82 (*ddd*, 1H, *J* = 12.4, 8.4, 4.9 Hz, NCH₂CHH), 1.70 (*ddd*, 1H, *J* = 12.4, 9.1, 8.4, 6.9 Hz, NCH₂CHH), 1.35 (*t*, 3H, *J* = 7.2 Hz, OCH₂CH₃), 1.33 (*t*, 3H, *J* = 7.1 Hz, OCH₂CH₃). ¹³C-NMR (100 MHz, CDCl₃): 169.7 (CO), 169.2 (CO), 167.0 (CO), 146.0 (C_{ar}), 140.0 (C_{ar}), 129.7

($2\times\text{CH}_{\text{ar}}$), 129.0 ($2\times\text{CH}_{\text{ar}}$), 128.3 ($2\times\text{CH}_{\text{ar}}$), 128.2 ($2\times\text{CH}_{\text{ar}}$), 128.1 (C_{ar}), 126.8 (CH_{ar}), 78.0 (C), 61.3 (CH_2O), 61.0 (CH_2O), 55.4 (CH_2), 52.0 (OCH_3), 50.6 (CH_2), 47.4 (CH), 37.6 (CH_2), 27.7 (CH_2), 14.4 (CH_3), 14.3 (CH_3). IR (film): 2979w, 2904w, 2840w, 1723s, 1609w, 1415w, 1367w, 1278s, 1202w, 1108w, 1020w, 968w, 758w, 700w. MS (ESI+): 454.23 (100, $[\text{M}+\text{H}]^+$), 476.21 (87, $[\text{M}+\text{Na}]^+$), 929.45 (58, $[2\text{M}+\text{Na}]^+$). HRMS (ESI): calculated for $\text{C}_{26}\text{H}_{32}\text{NO}_6$ ($[\text{M}+\text{H}]^+$) 454.2224, found 454.2224.

Diethyl 1-benzyl-3-(4-(*tert*-butyldimethylsilyloxy)-2-methylenebutyl)pyrrolidine-2,2-dicarboxylate **15d**

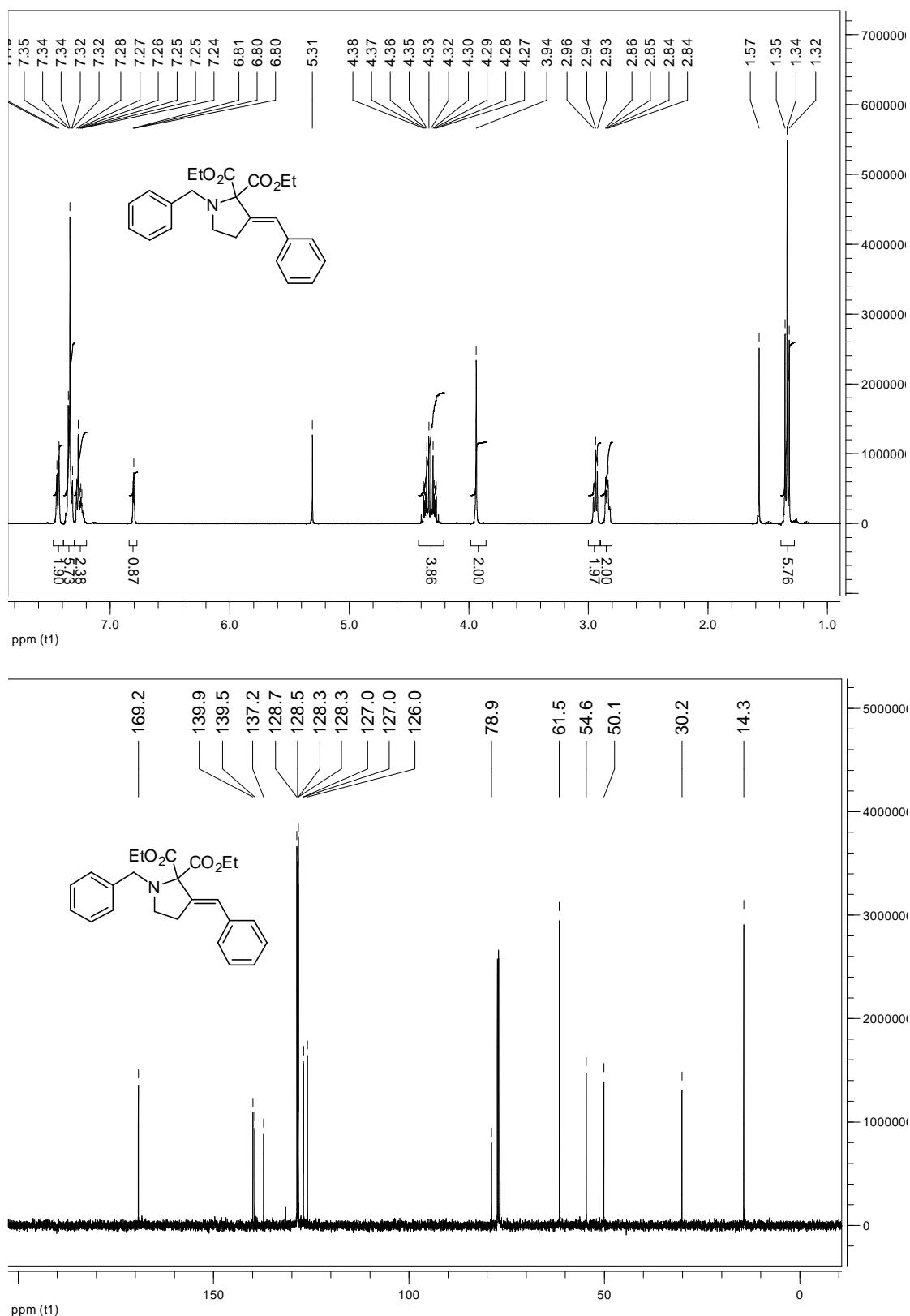


To a solution of diethyl 2-(benzyl(but-3-enyl)amino)malonate **14** (160 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) were added Pd(dppf)Cl₂ (20 mg, 5.0 mol%) and *tert*-butyl(3-iodobut-3-enyloxy)dimethylsilane (234 mg, 0.75 mmol, 1.5 eq.) followed dropwise by NaHMDS solution (0.83 mL, 0.6 M in toluene, 0.5 mmol, 1.0 eq.). The reaction was stirred at 60 °C for 15 h, filtered through a pad of silica (eluent: Et₂O) and the solvent removed. Purification by FC (PE/Et₂O 8:1) afforded diethyl 1-benzyl-3-(4-(*tert*-butyldimethylsilyloxy)-2-methylenebutyl)pyrrolidine-2,2-dicarboxylate **15d** (83.2 mg, 0.17 mmol, 33%) as a colorless oil.

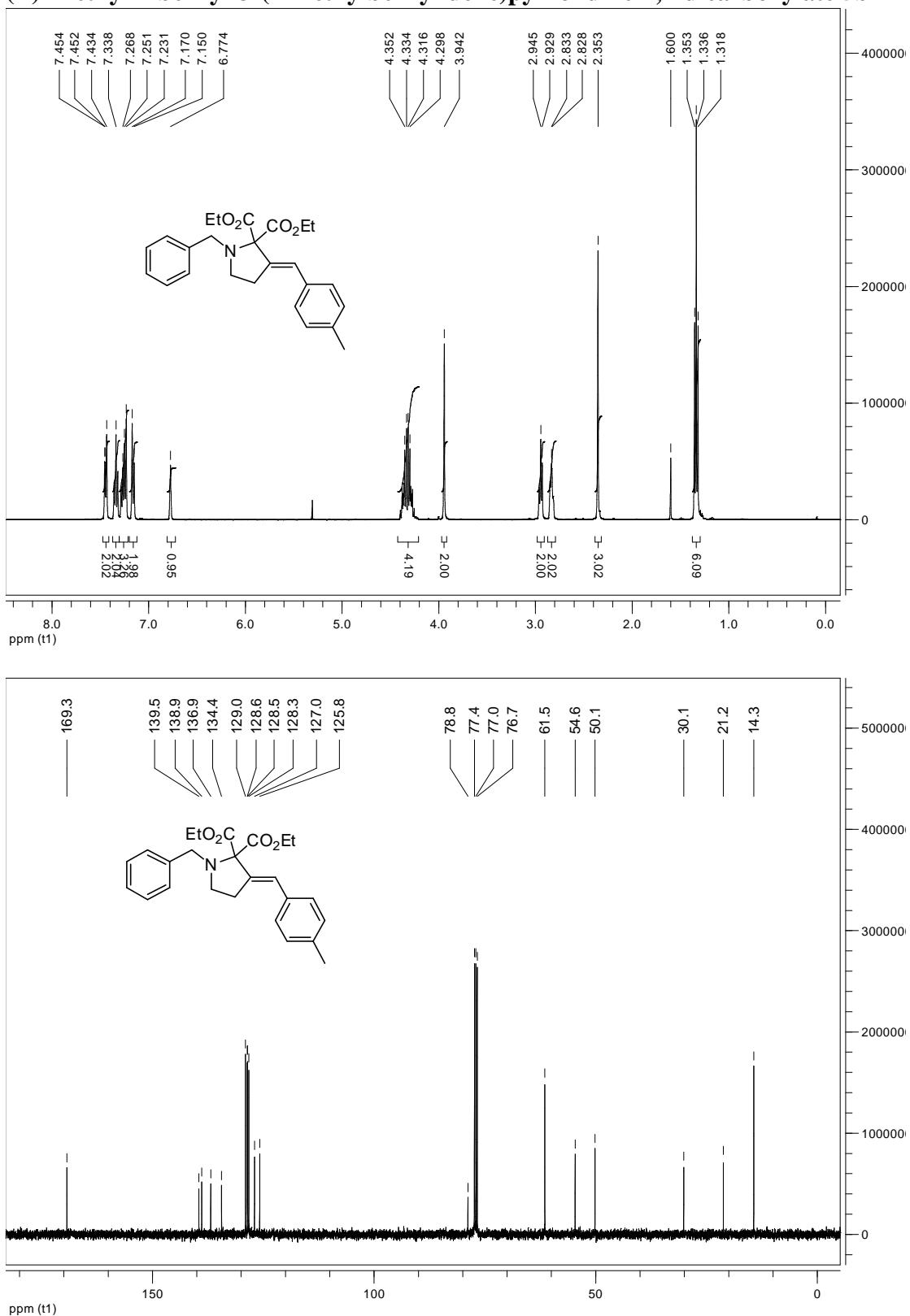
¹H-NMR (400 MHz, CDCl₃): 7.40-7.39 (*m*, 2H, H_{ar}), 7.32-7.29 (*m*, 2H, H_{ar}), 7.25-7.21 (*m*, 1H, H_{ar}), 4.81 (*s*, 1H, H_{olef}), 4.80 (*s*, 1H, H_{olef}), 4.34-4.21 (*m*, 4H, 2xCH₂O), 4.00 (*d*, 1H, *J* = 13.4 Hz, CHHPh), 3.79 (*d*, 1H, *J* = 13.4 Hz, CHHPh), 3.76-3.66 (*m*, 2H, CH₂OTBS), 2.89 (*dtd*, 1H, *J* = 11.7, 8.3, 3.0 Hz, CH), 2.83-2.79 (*m*, 2H, CH₂N), 2.46 (*d*, 1H, *J* = 13.6 Hz, CHCHHC=C), 2.24 (*t*, 2H, *J* = 7.4 Hz, CH₂), 2.04-1.92 (*m*, 2H, CHCHHC=C and NCH₂CHH), 1.70-1.61 (*m*, 1H, NCH₂CHH), 1.32 (*t*, 3H, *J* = 7.2 Hz, CH₃), 1.31 (*t*, 3H, *J* = 7.2 Hz, CH₃), 0.89 (*s*, 9H, C(CH₃)₃), 0.05 (*s*, 6H, Si(CH₃)₂). ¹³C-NMR (100 MHz, CDCl₃): 169.8 (CO), 169.3 (CO), 144.3 (C_{olef}), 140.1 (C_{ar}), 128.3 ($2\times\text{CH}_{\text{ar}}$), 128.1 ($2\times\text{CH}_{\text{ar}}$), 126.7 (CH_{ar}), 112.5 (CH_{2olef}), 78.1 (C), 62.0 (CH₂O), 61.1 (CH₂O), 60.8 (CH₂O), 55.4 (CH₂Ph), 50.6 (CH₂), 43.7 (CH₂), 38.8 (CH₂), 38.3 (CH₂), 27.7 (C), 25.9 (3xCH₃), 18.3 (CH), 14.4 (CH₃), 14.2 (CH₃), -5.3 (Si(CH₃)₂). IR (film): 2955m, 2930m, 2856m, 1729s, 1471w, 1463w, 1454w, 1255m, 1203m, 1141w, 1096s, 1030m, 835s, 775m, 699w. MS (ESI+): 504.28 (93, $[\text{M}+\text{H}]^+$), 526.26 (100, $[\text{M}+\text{Na}]^+$). HRMS (ESI): calculated for $\text{C}_{28}\text{H}_{45}\text{NNaO}_5\text{Si}$ ($[\text{M}+\text{Na}]^+$) 526.2959, found 526.2963.

3. ^1H and ^{13}C NMR spectra of the cyclization products

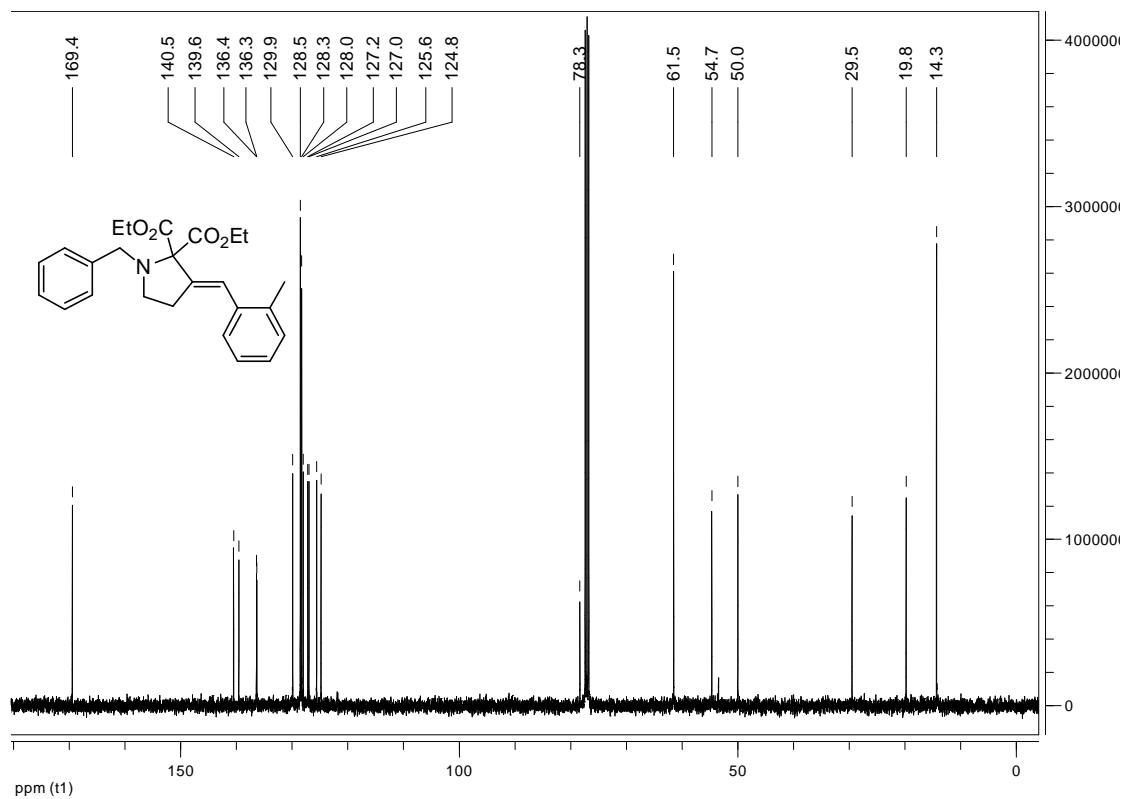
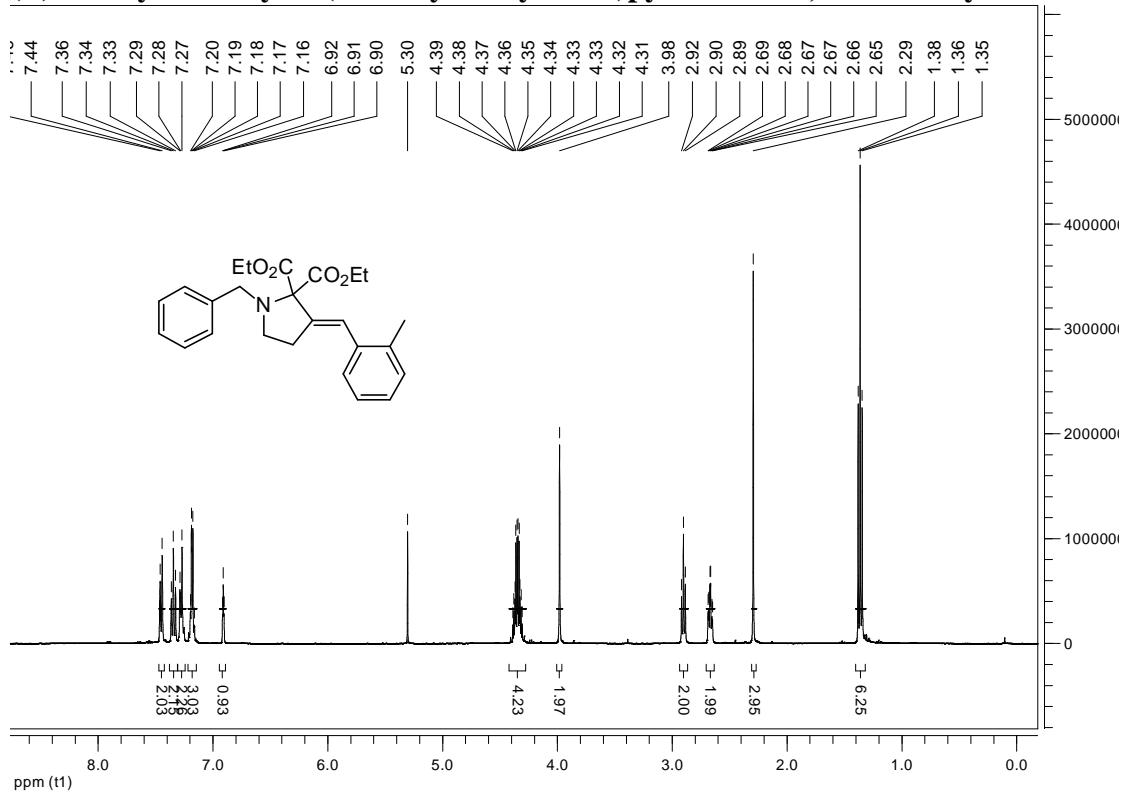
(E)-Diethyl 1-benzyl-3-benzylidenepyrrolidine-2,2-dicarboxylate 5a



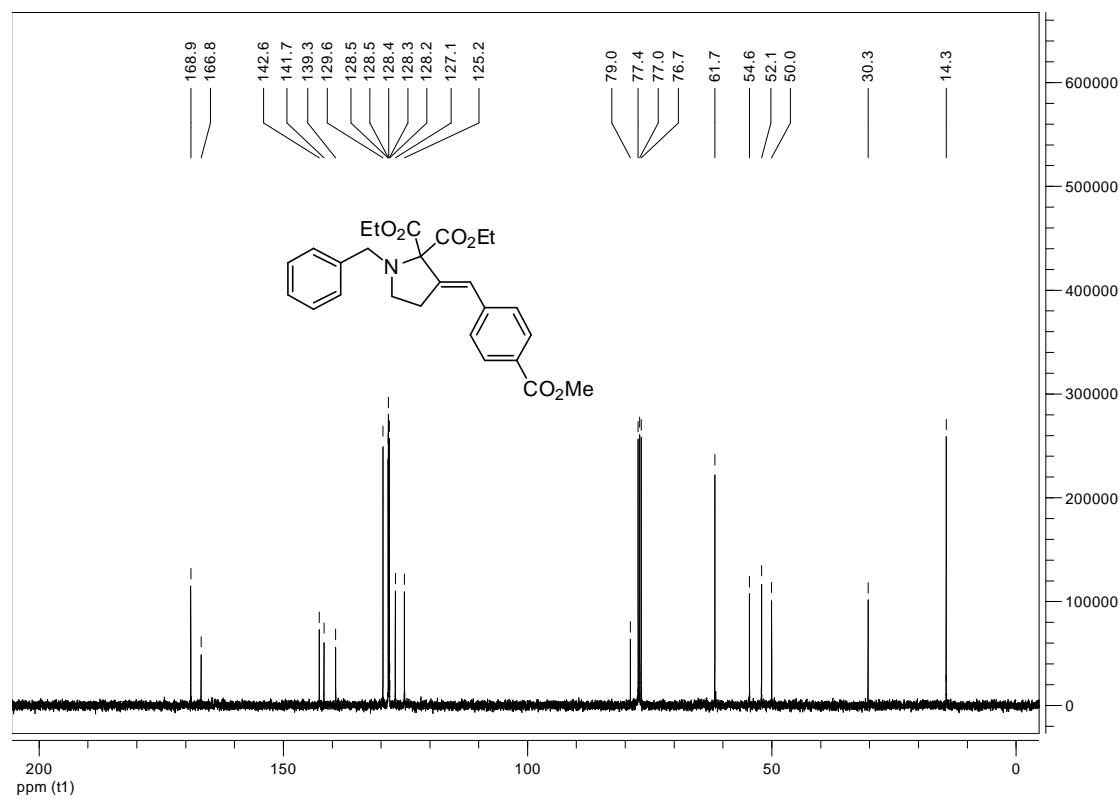
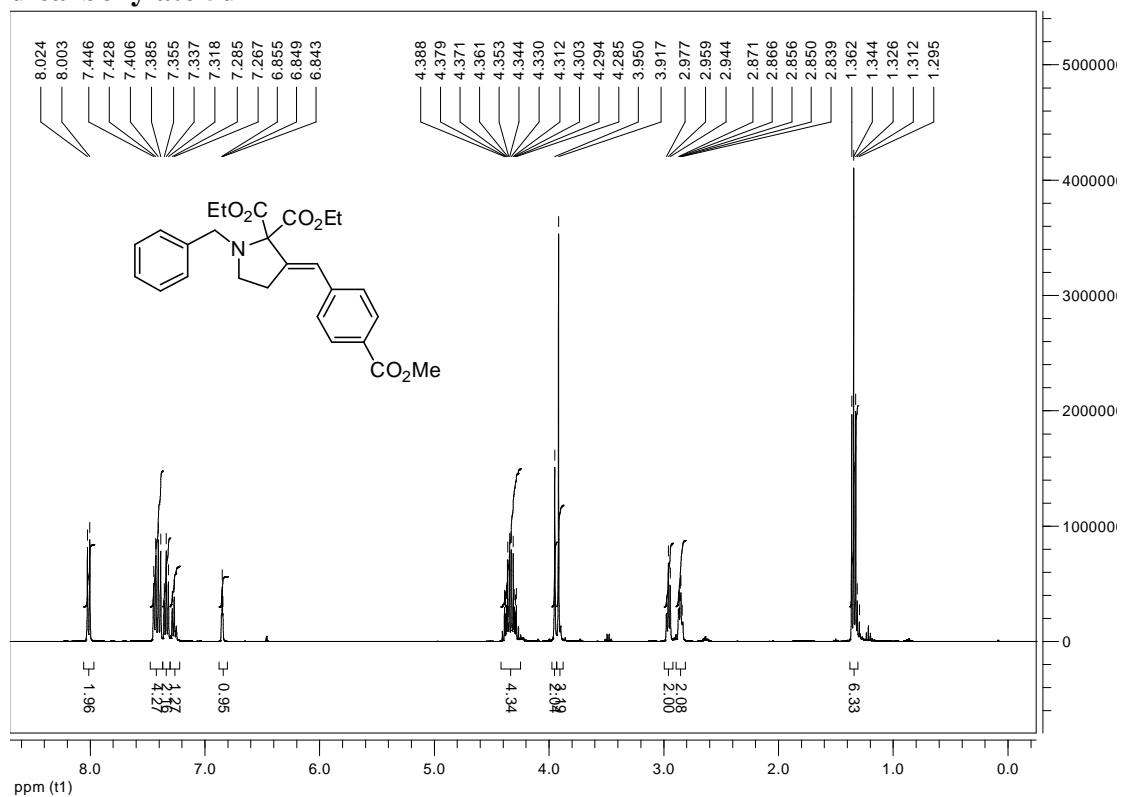
(E)-Diethyl 1-benzyl-3-(4-methylbenzylidene)pyrrolidine-2,2-dicarboxylate 5b



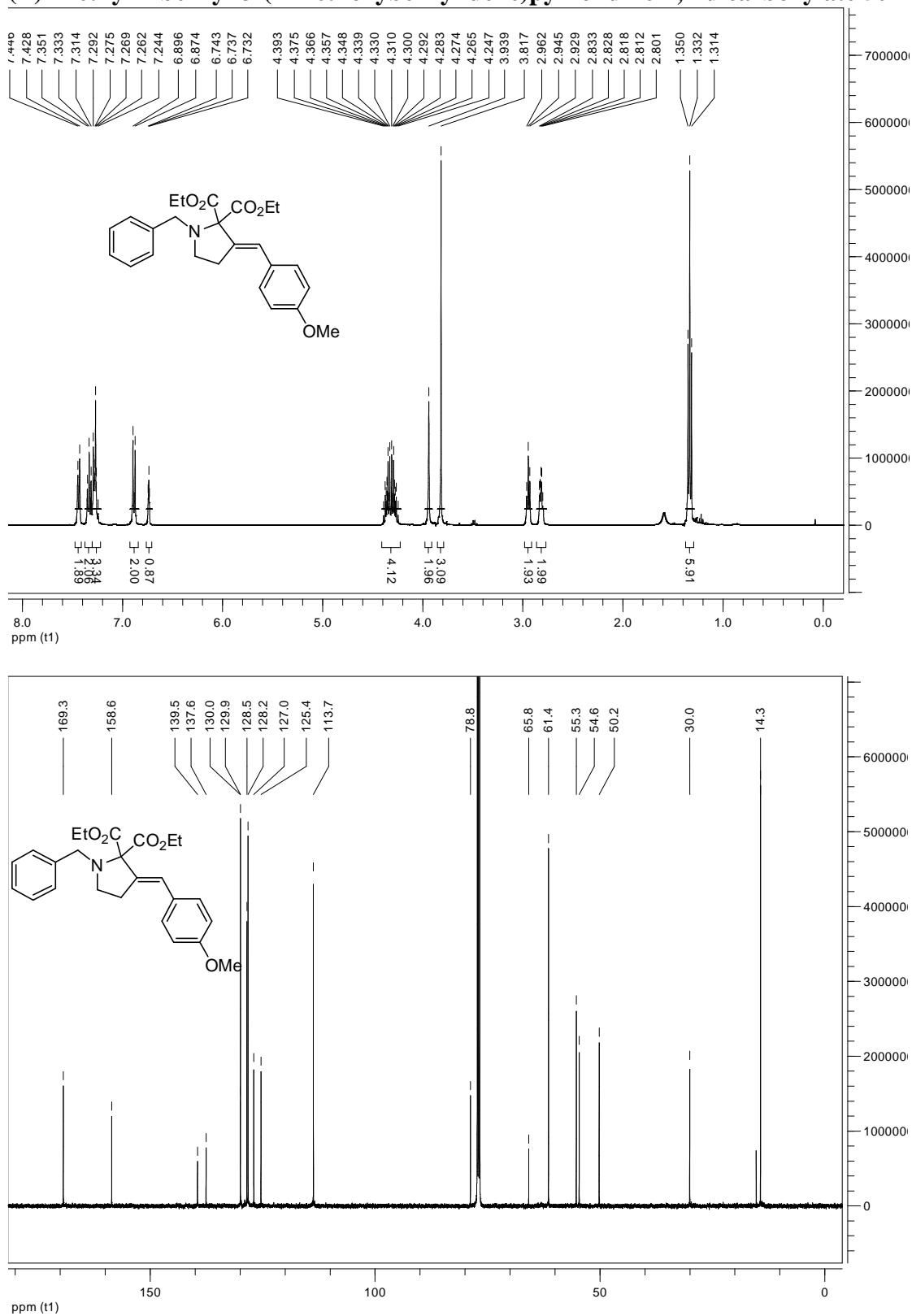
(E)-Diethyl 1-benzyl-3-(2-methylbenzylidene)pyrrolidine-2,2-dicarboxylate 5c



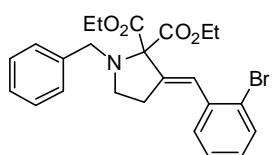
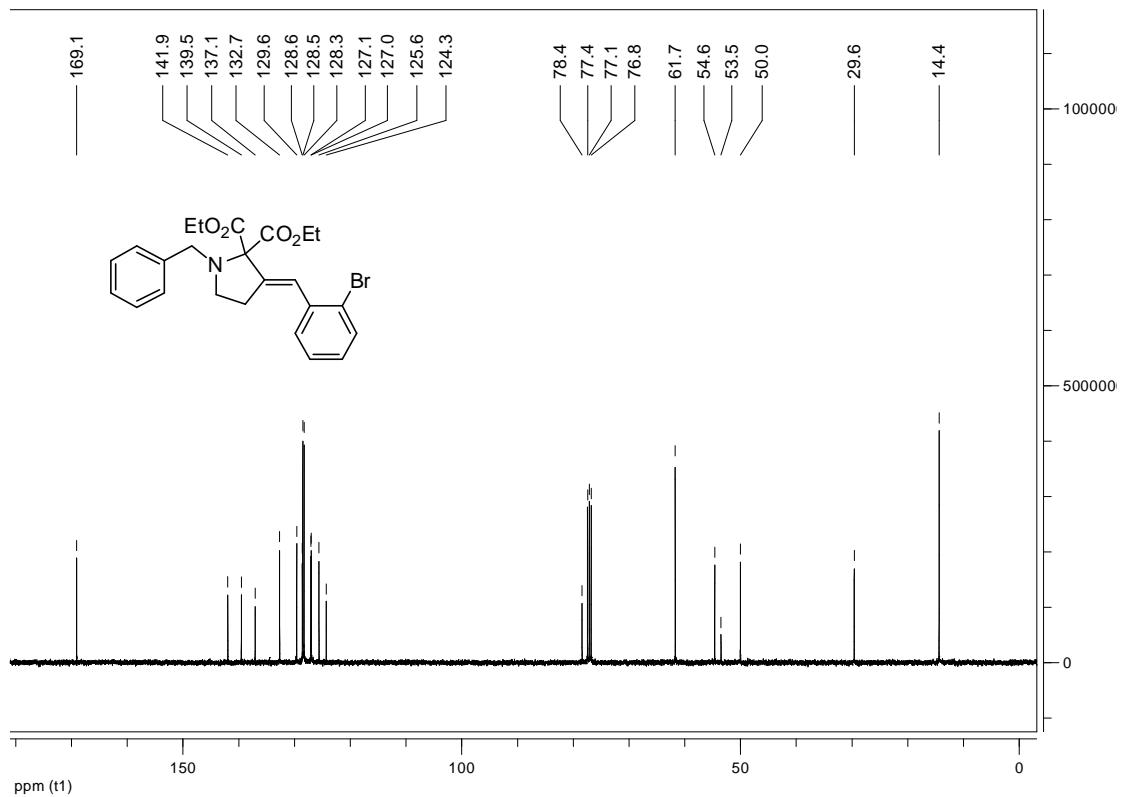
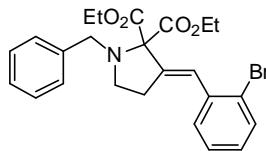
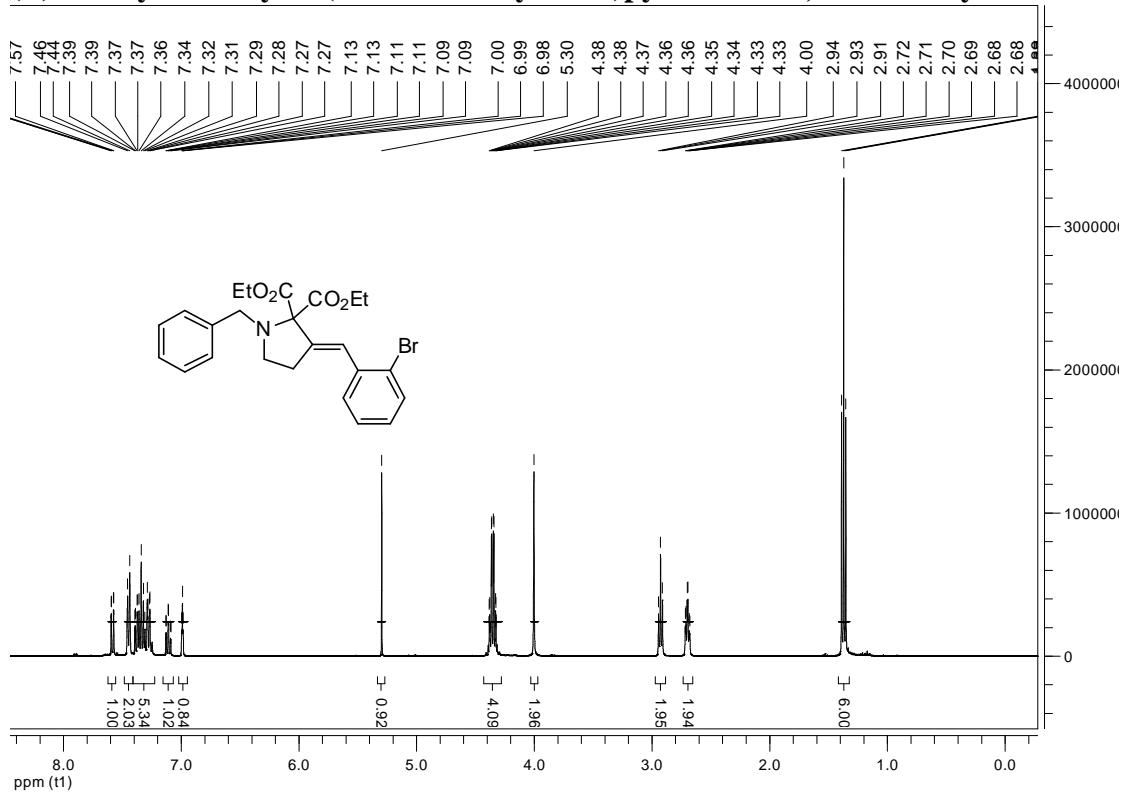
(E)-Diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzylidene)pyrrolidine-2,2-dicarboxylate 5d



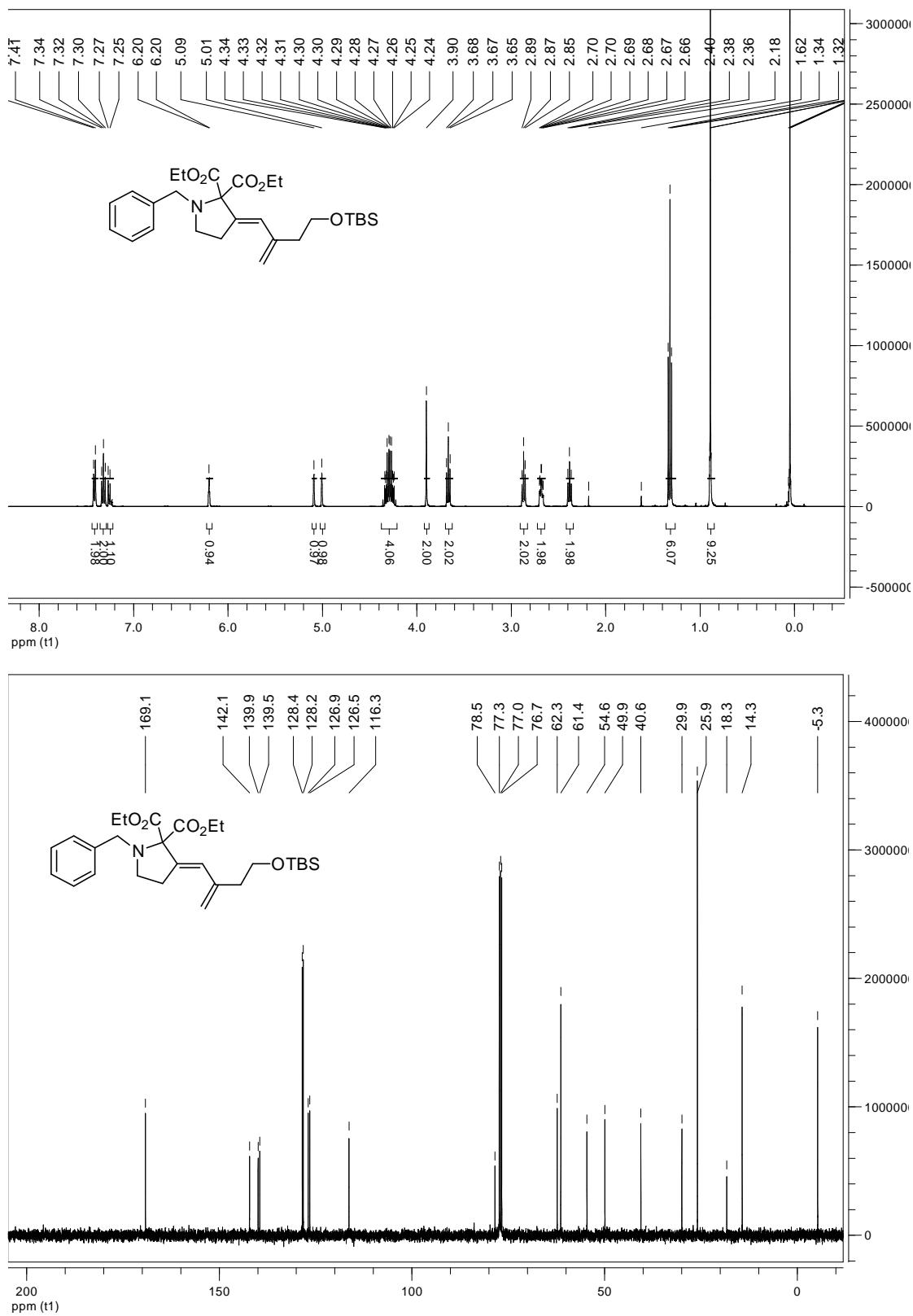
(E)-Diethyl 1-benzyl-3-(4-methoxybenzylidene)pyrrolidine-2,2-dicarboxylate 5e



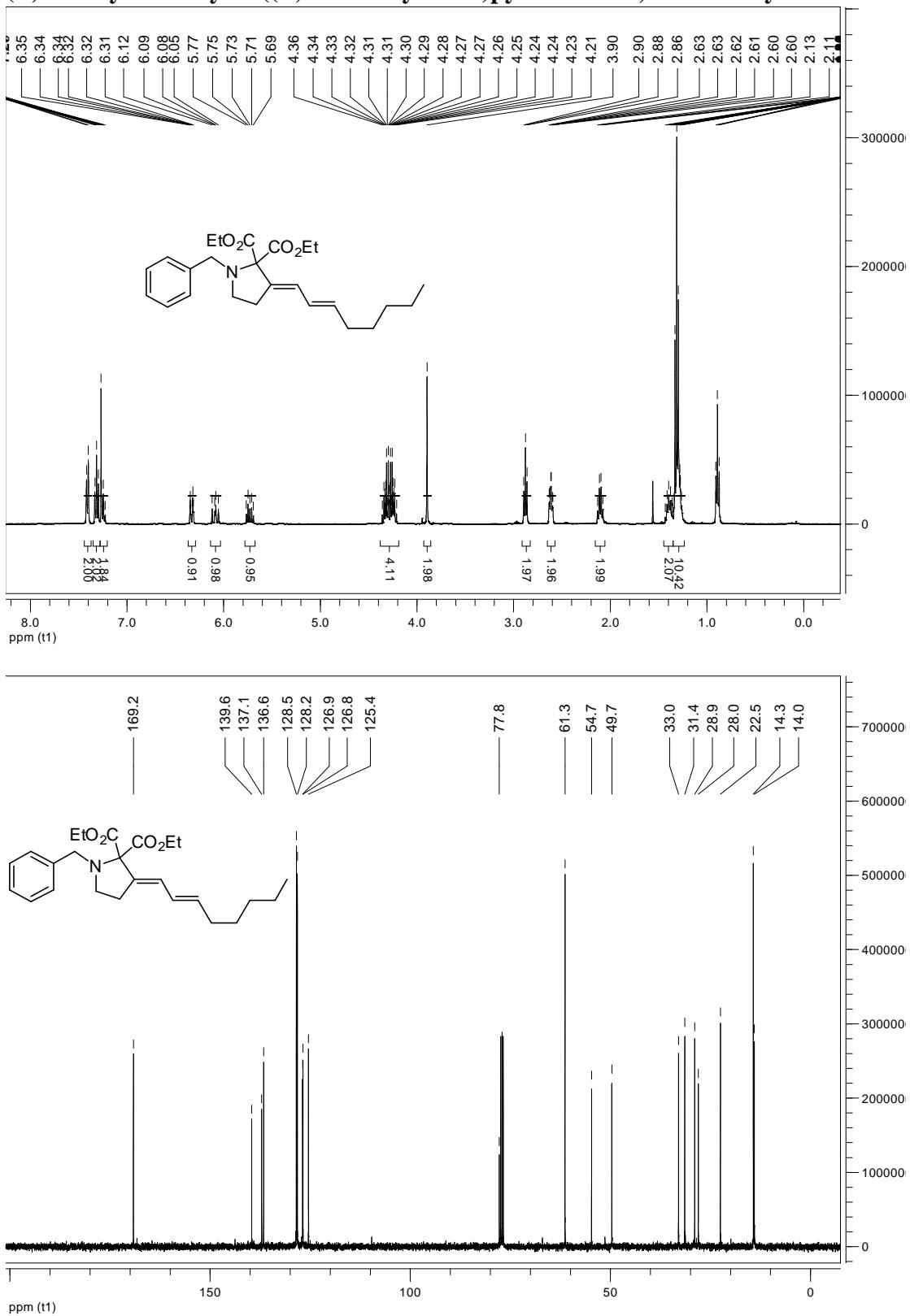
(E)-Diethyl 1-benzyl-3-(2-bromobenzylidene)pyrrolidine-2,2-dicarboxylate 5f



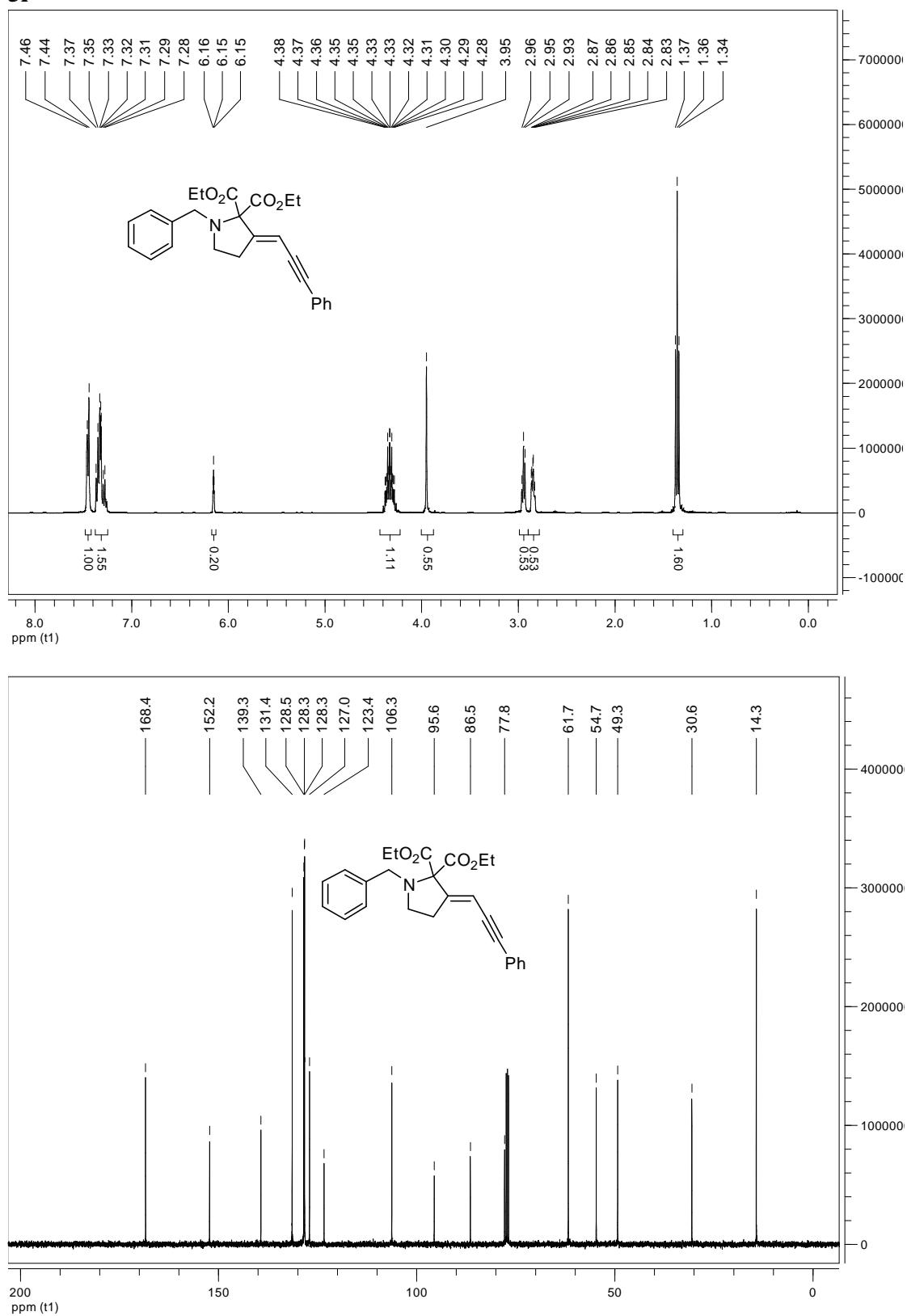
(E)-Diethyl 1-benzyl-3-(4-(tert-butyldimethylsilyloxy)-2-methylenebutylidene)pyrrolidine-2,2-dicarboxylate 5g



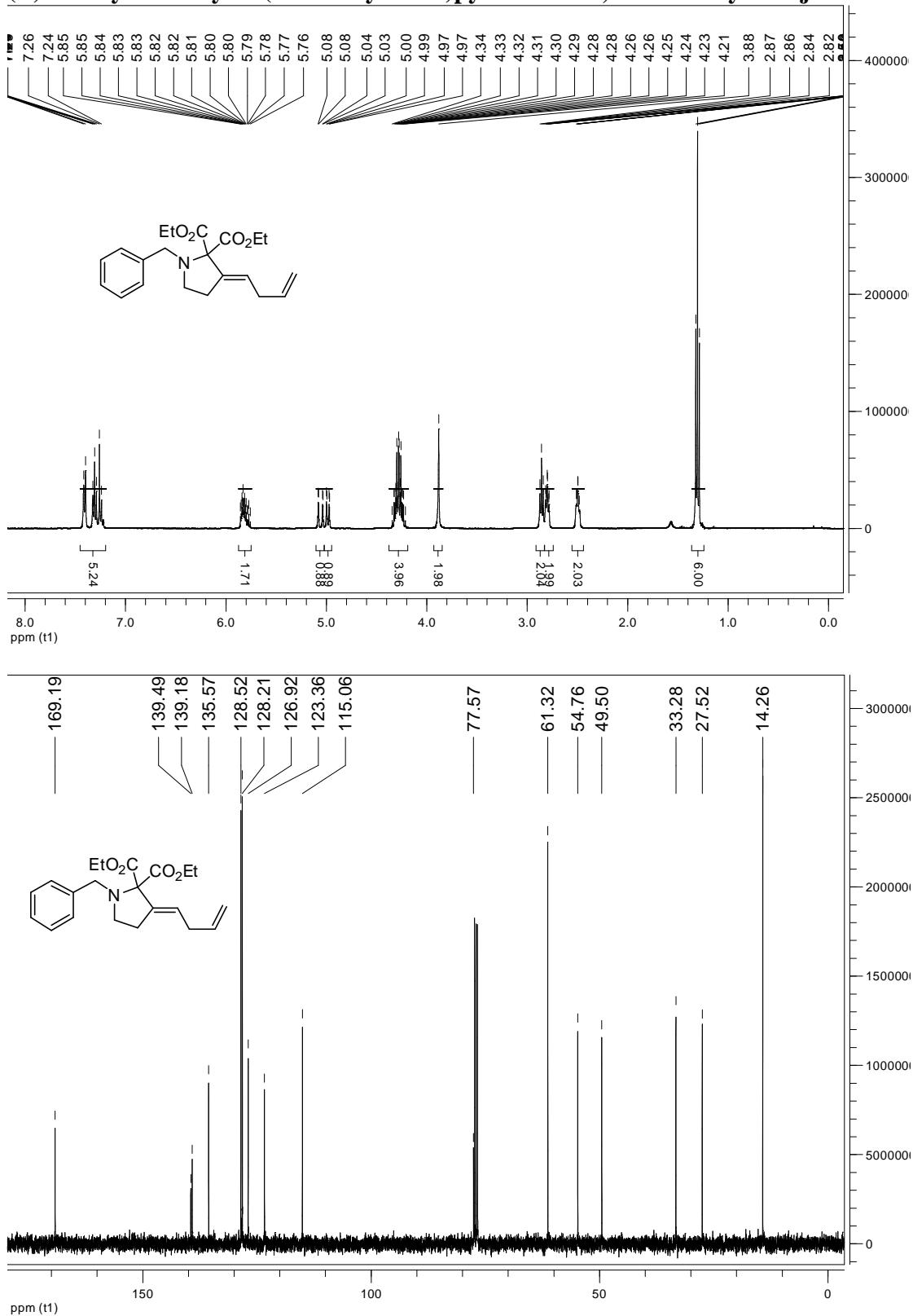
(E)-Diethyl 1-benzyl-3-((E)-oct-2-enylidene)pyrrolidine-2,2-dicarboxylate 5h



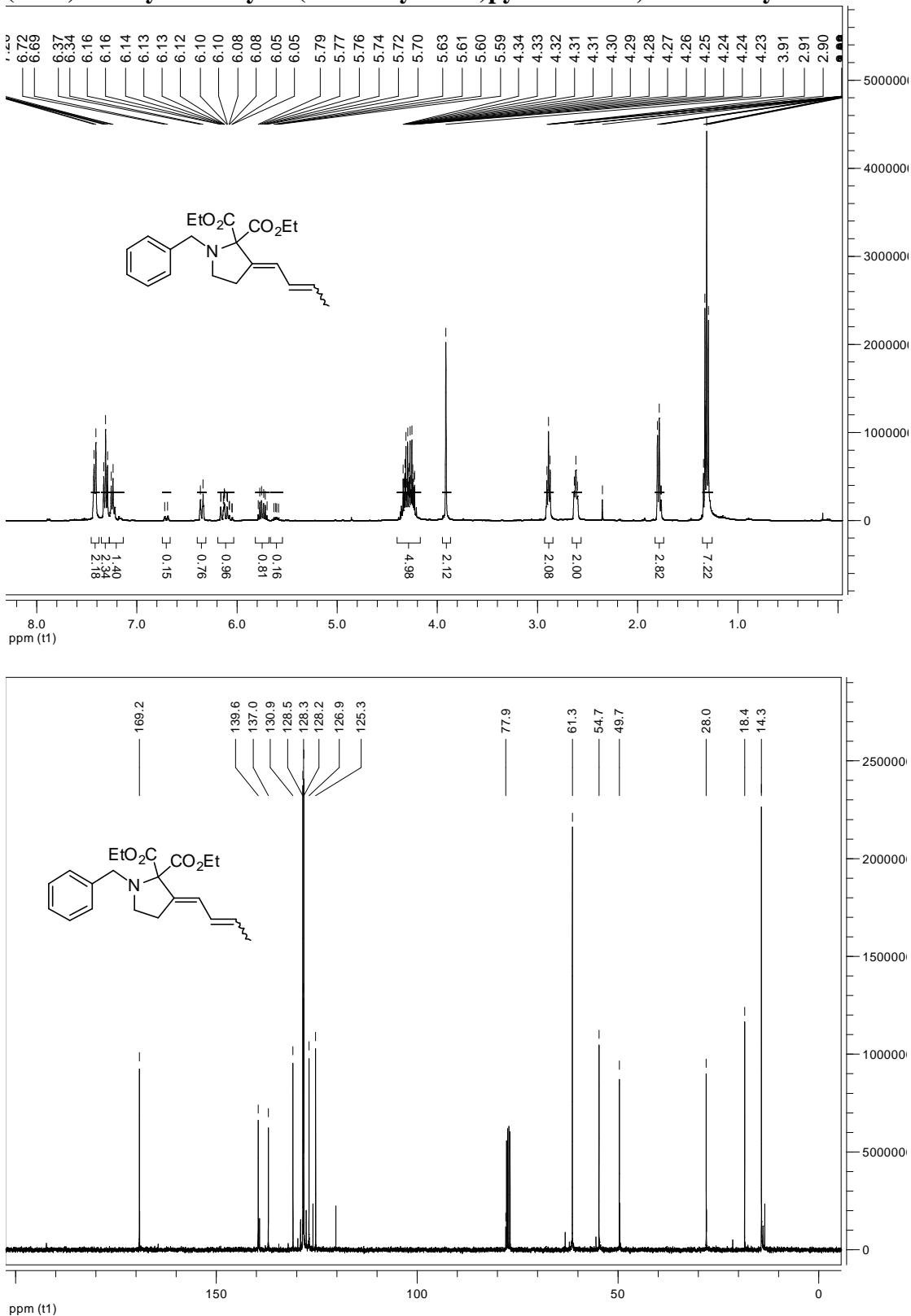
(E)-Diethyl 1-benzyl-3-(3-phenylprop-2-ynylidene)pyrrolidine-2,2-dicarboxylate
5i



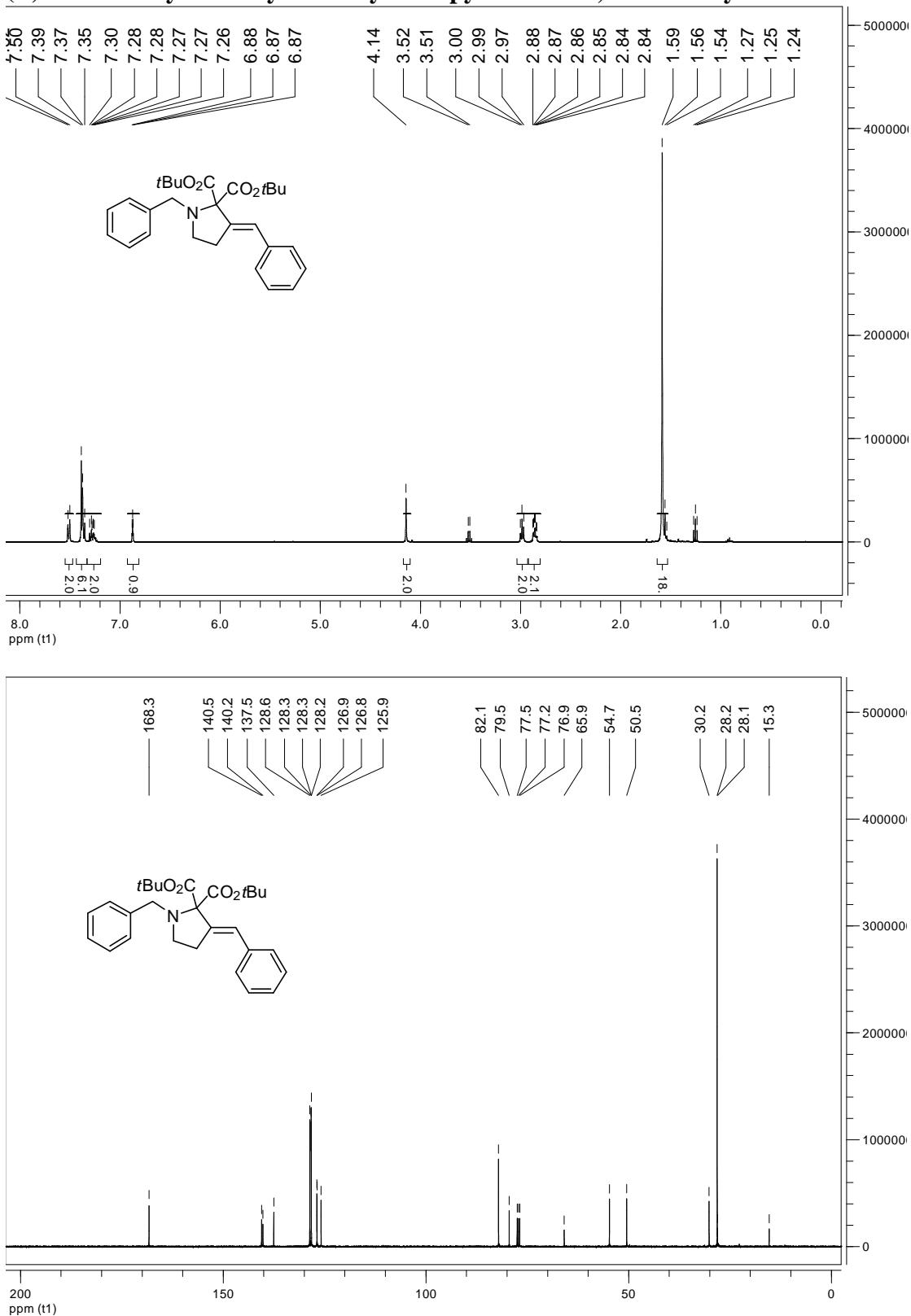
(E)-Diethyl 1-benzyl-3-(but-3-enylidene)pyrrolidine-2,2-dicarboxylate 5j



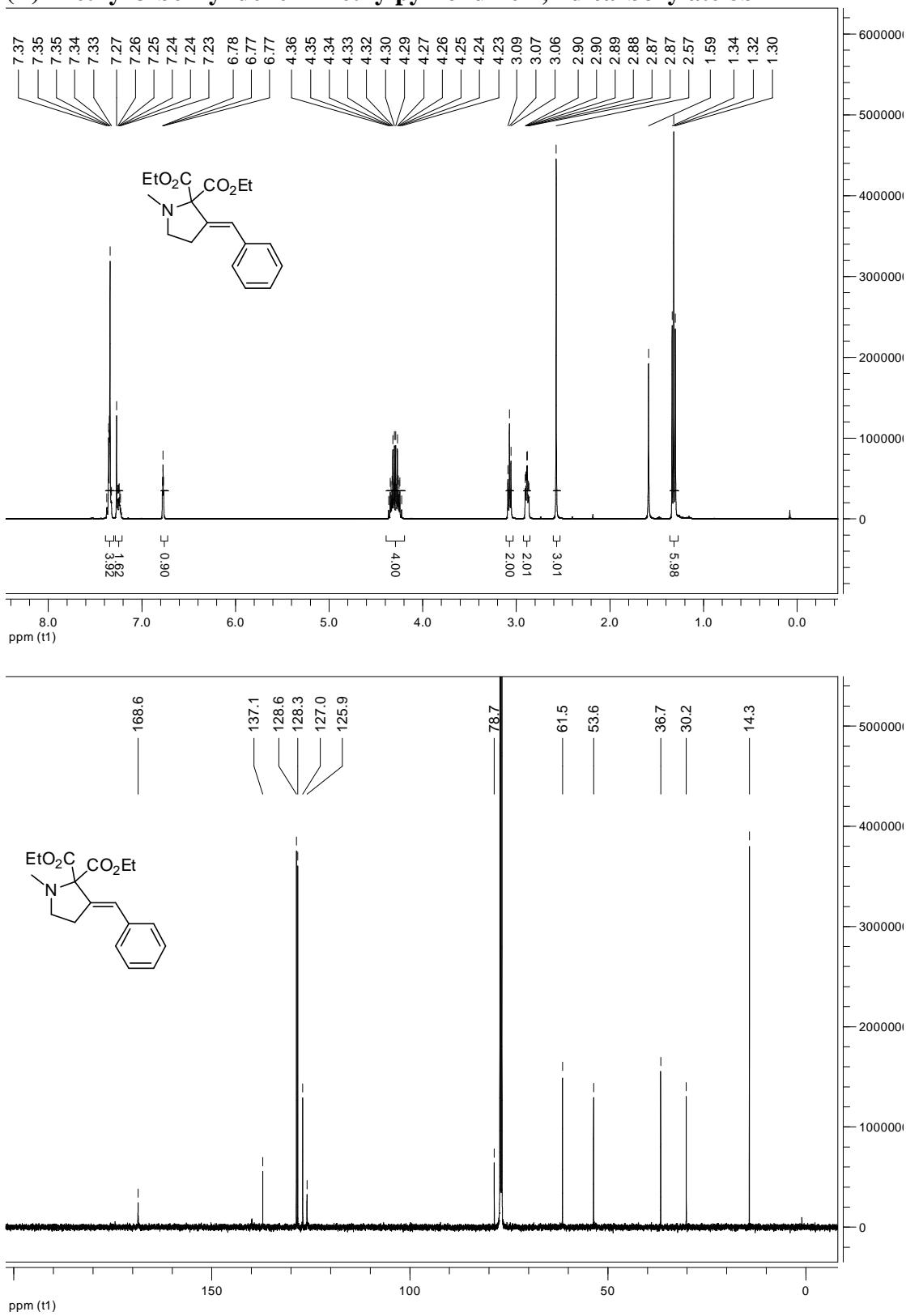
(3E/Z)-Diethyl 1-benzyl-3-(but-2-enylidene)pyrrolidine-2,2-dicarboxylate 5k



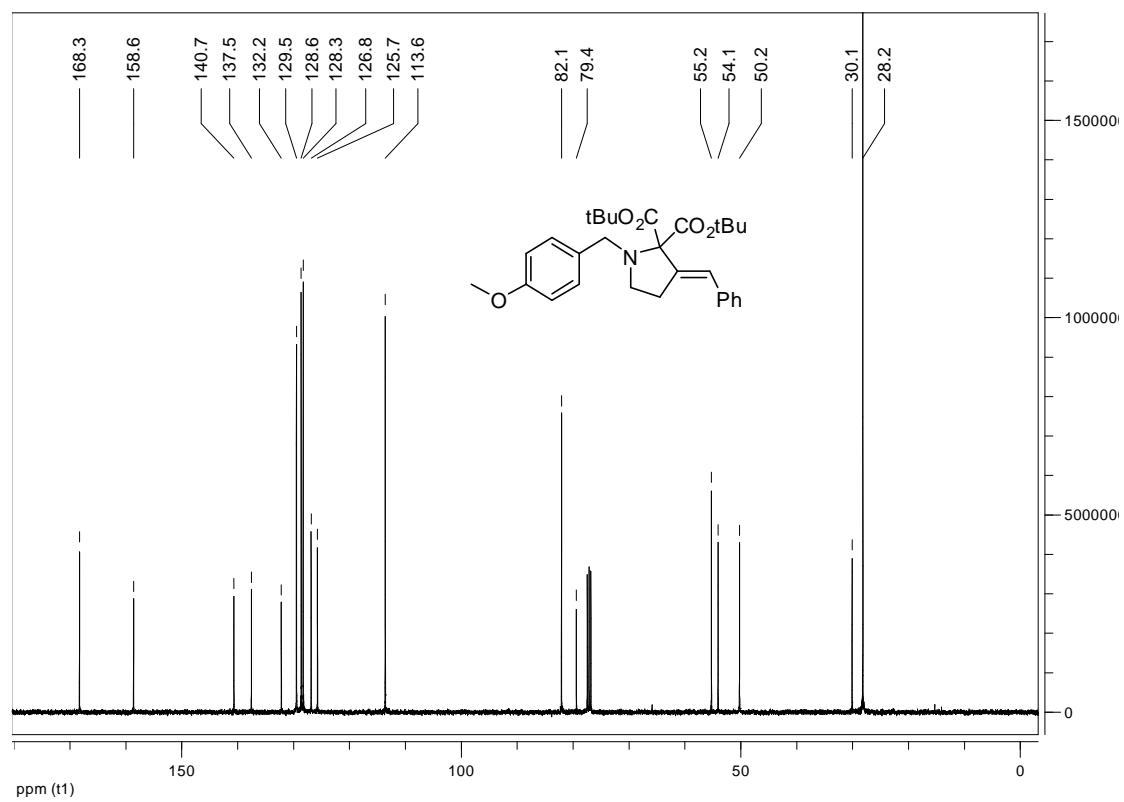
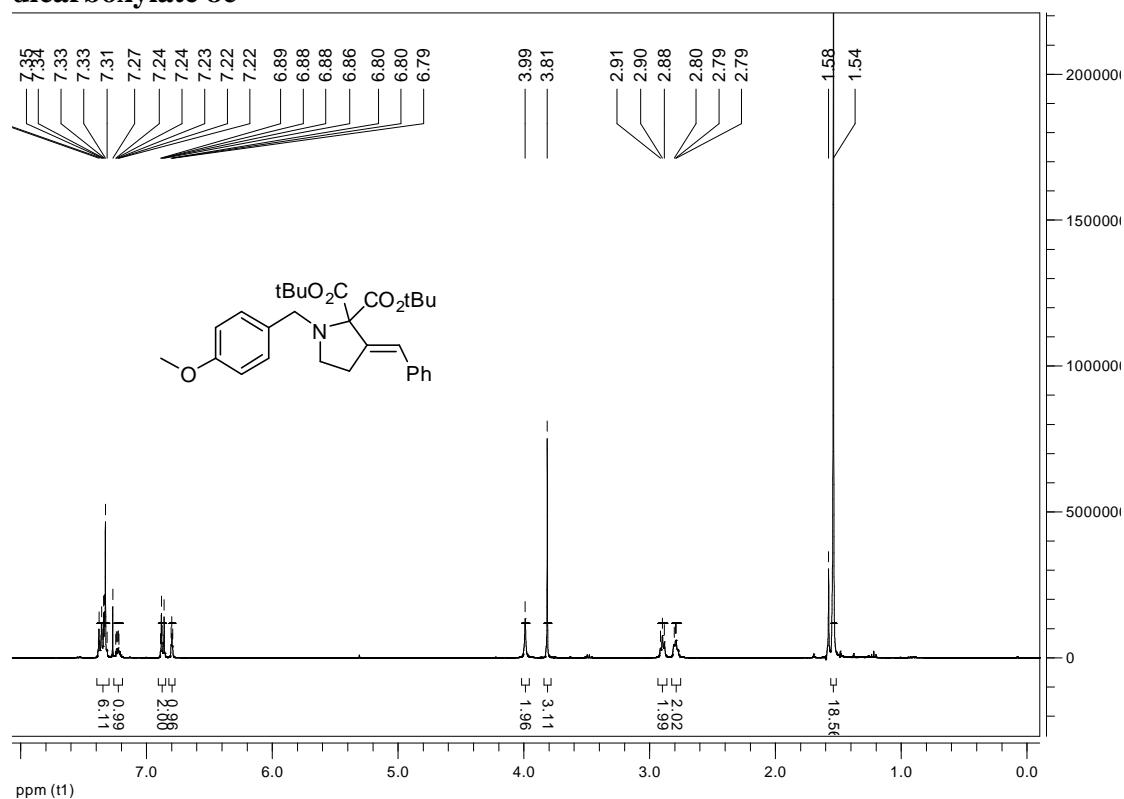
(E)-Di-*tert*-butyl 1-benzyl-3-benzylidenepyrrolidine-2,2-dicarboxylate 8a



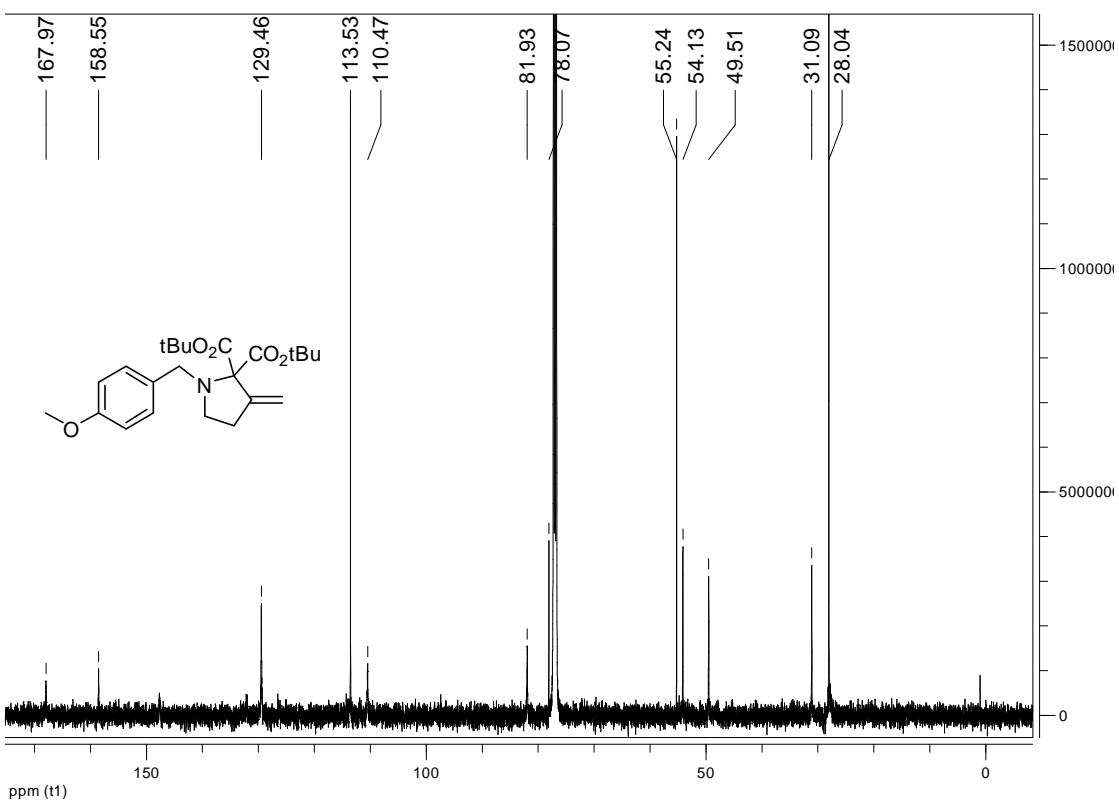
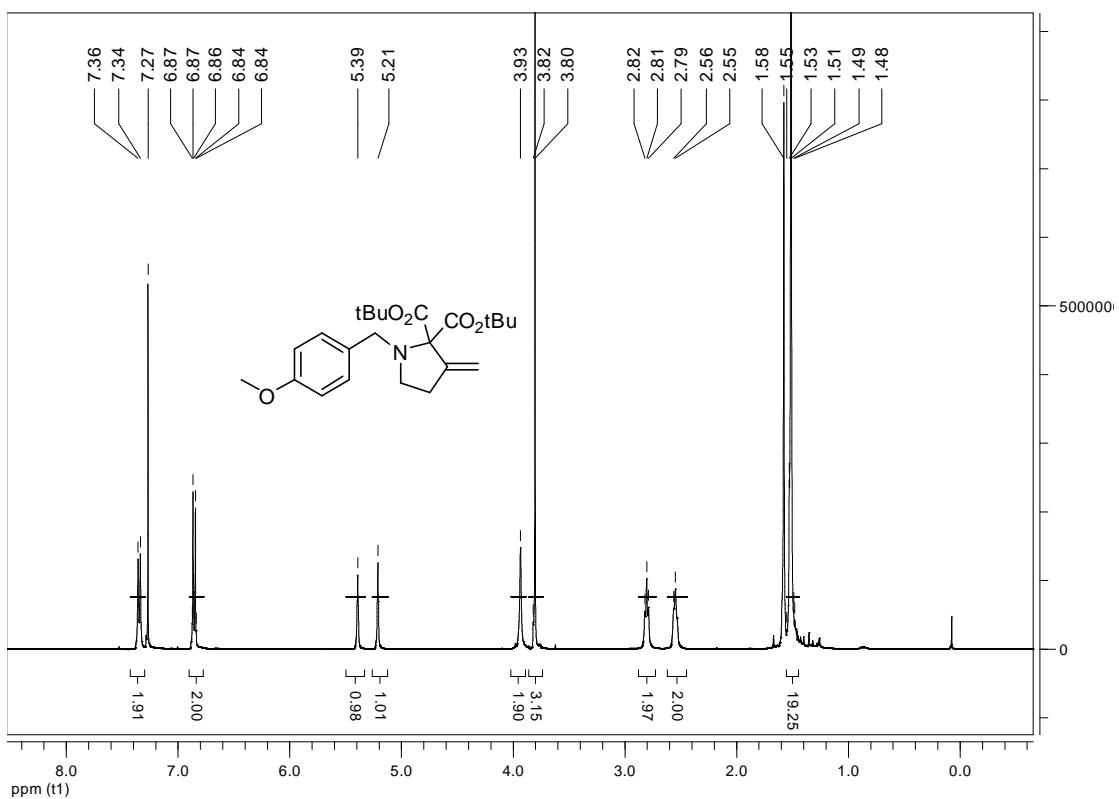
(E)-Diethyl 3-benzylidene-1-methylpyrrolidine-2,2-dicarboxylate 8b



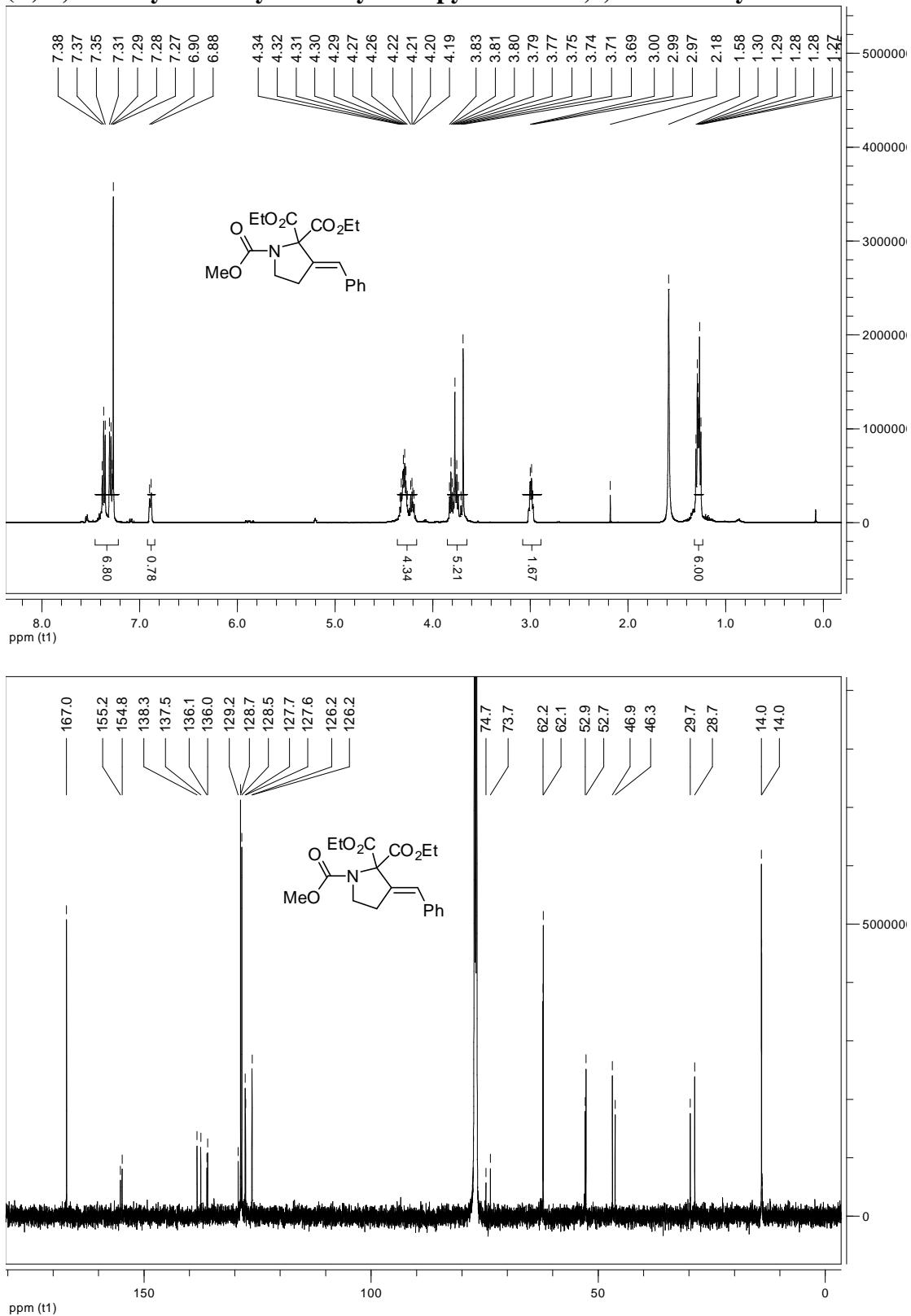
(E)-Di-*tert*-butyl 3-benzylidene-1-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate 8c



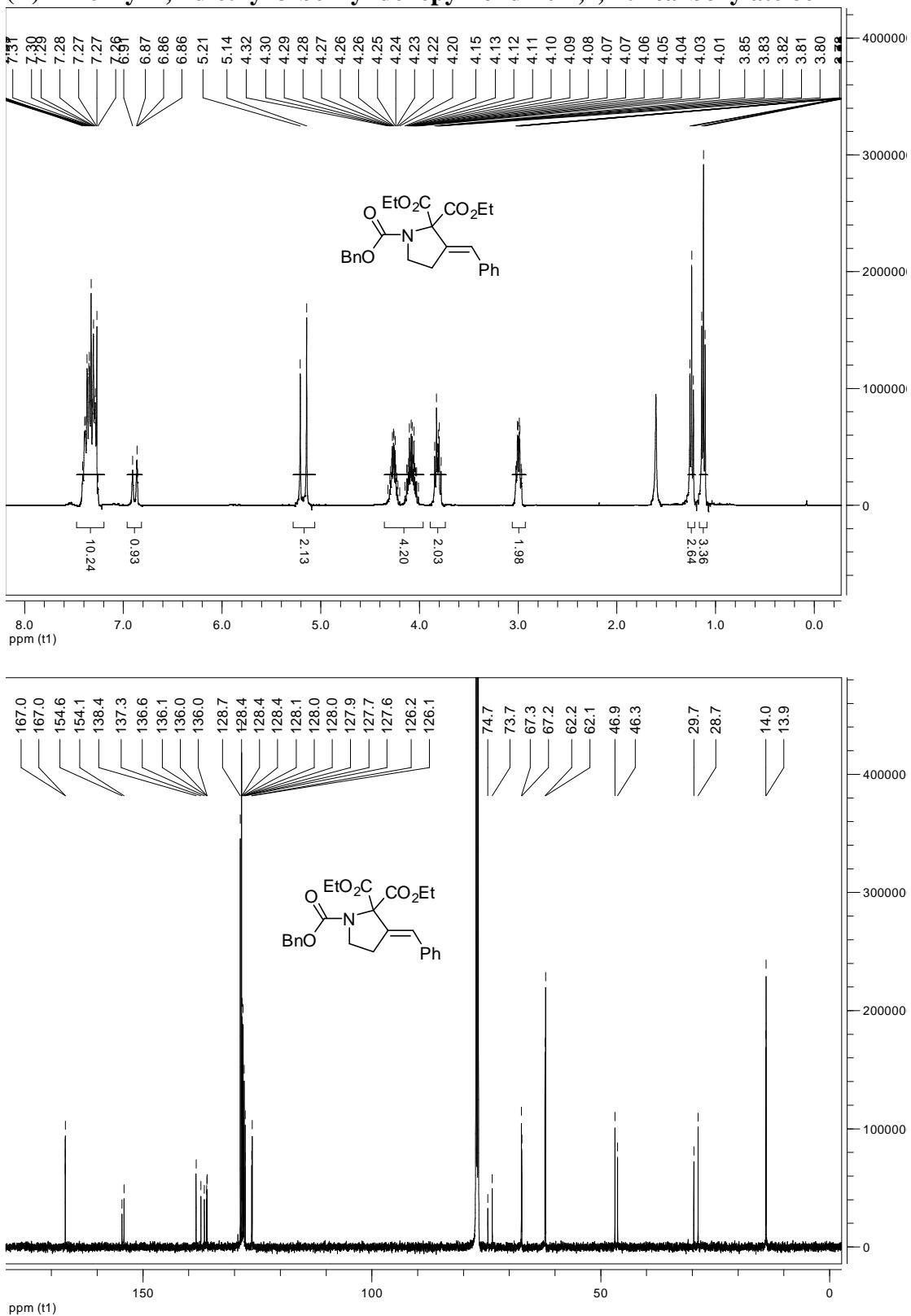
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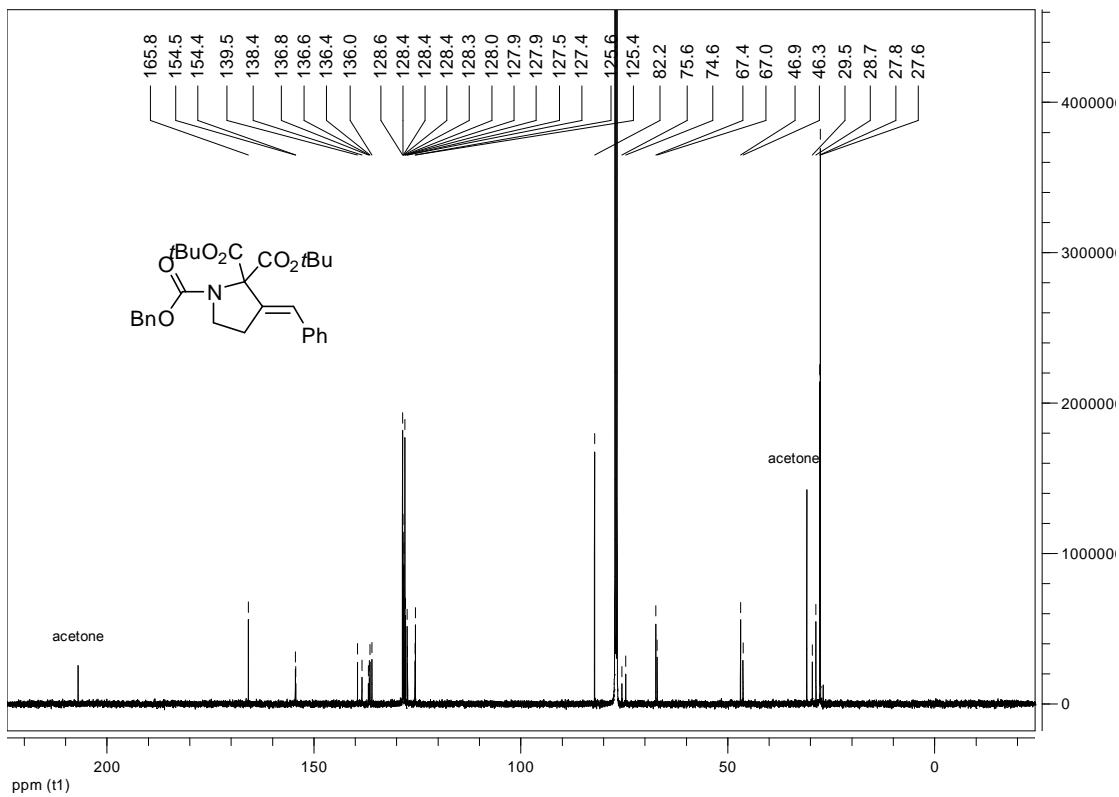
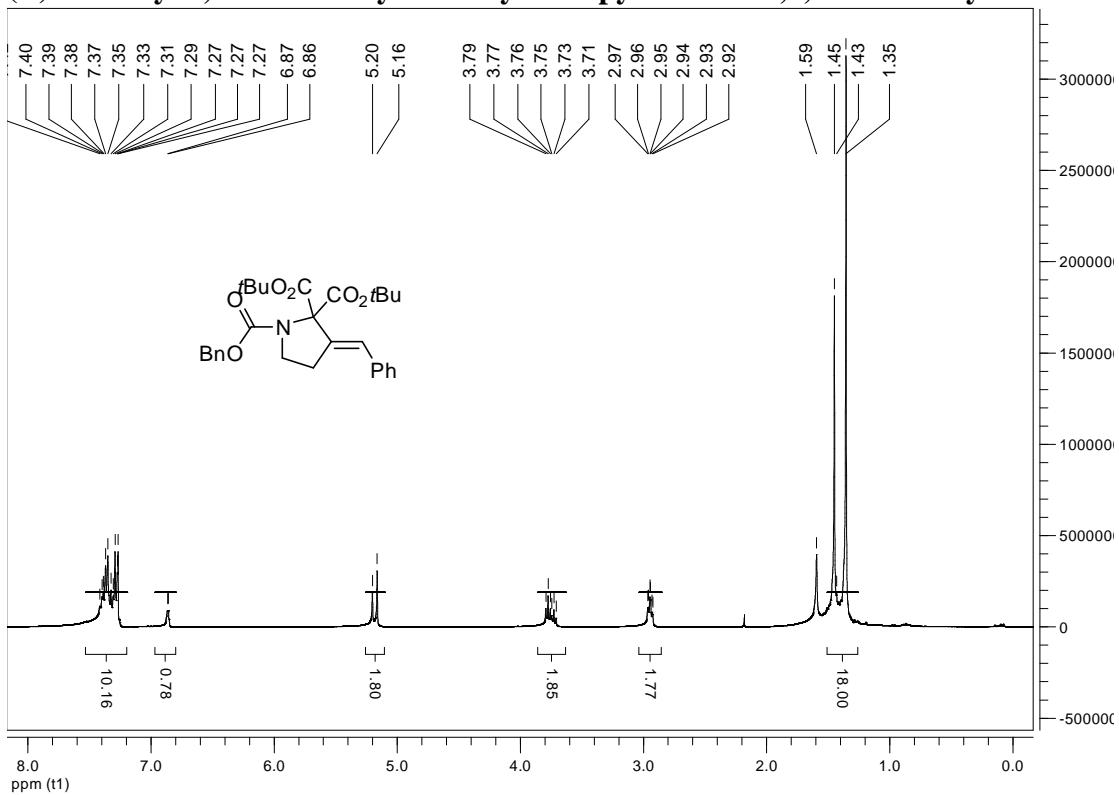
(E)-2,2-Diethyl 1-methyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8d



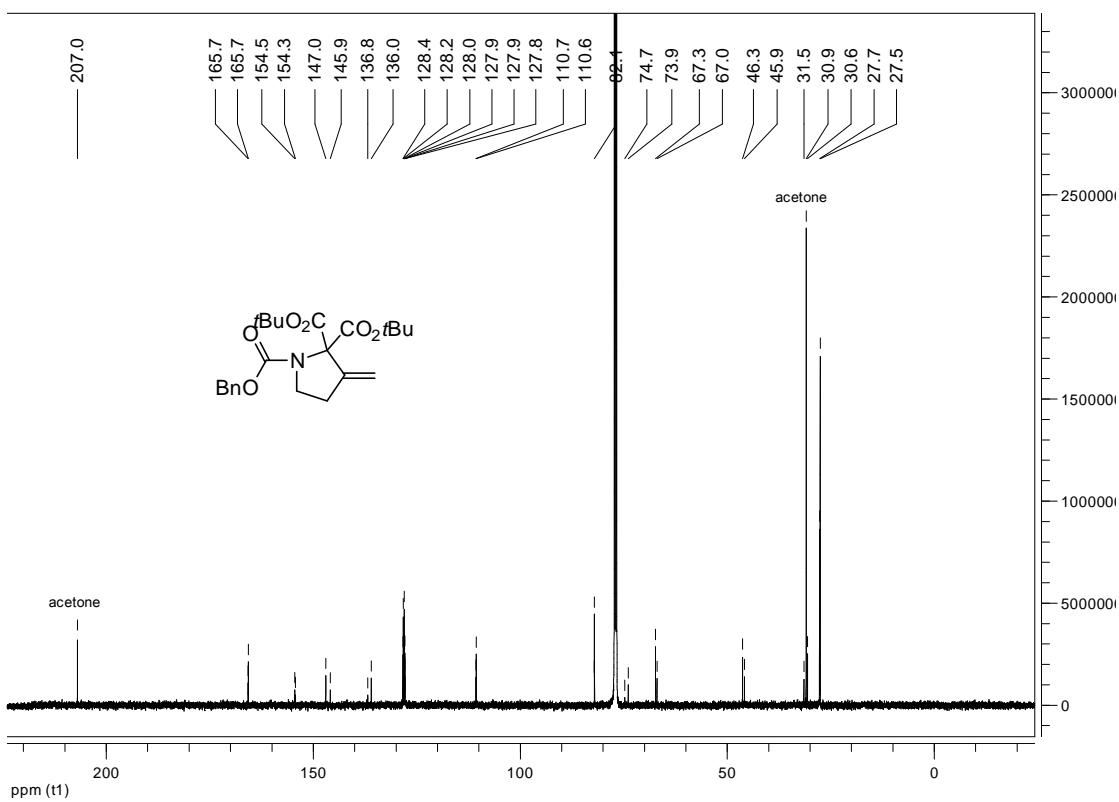
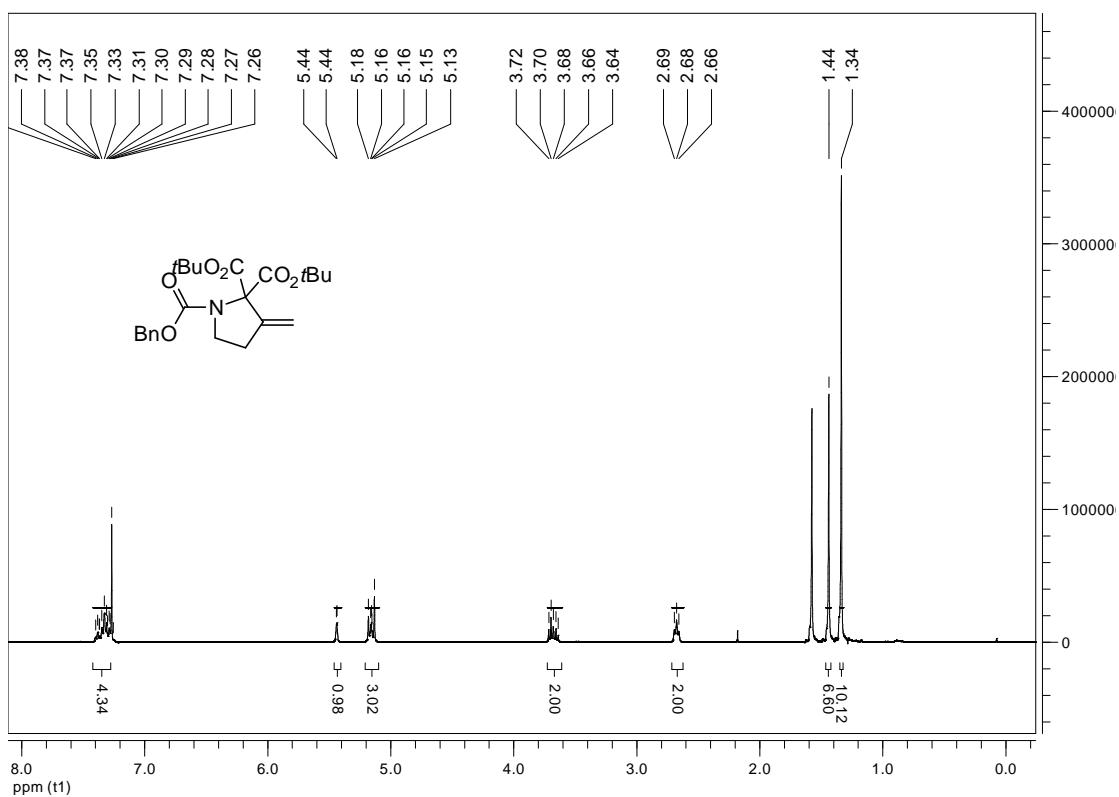
(E)-1-Benzyl 2,2-diethyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8e



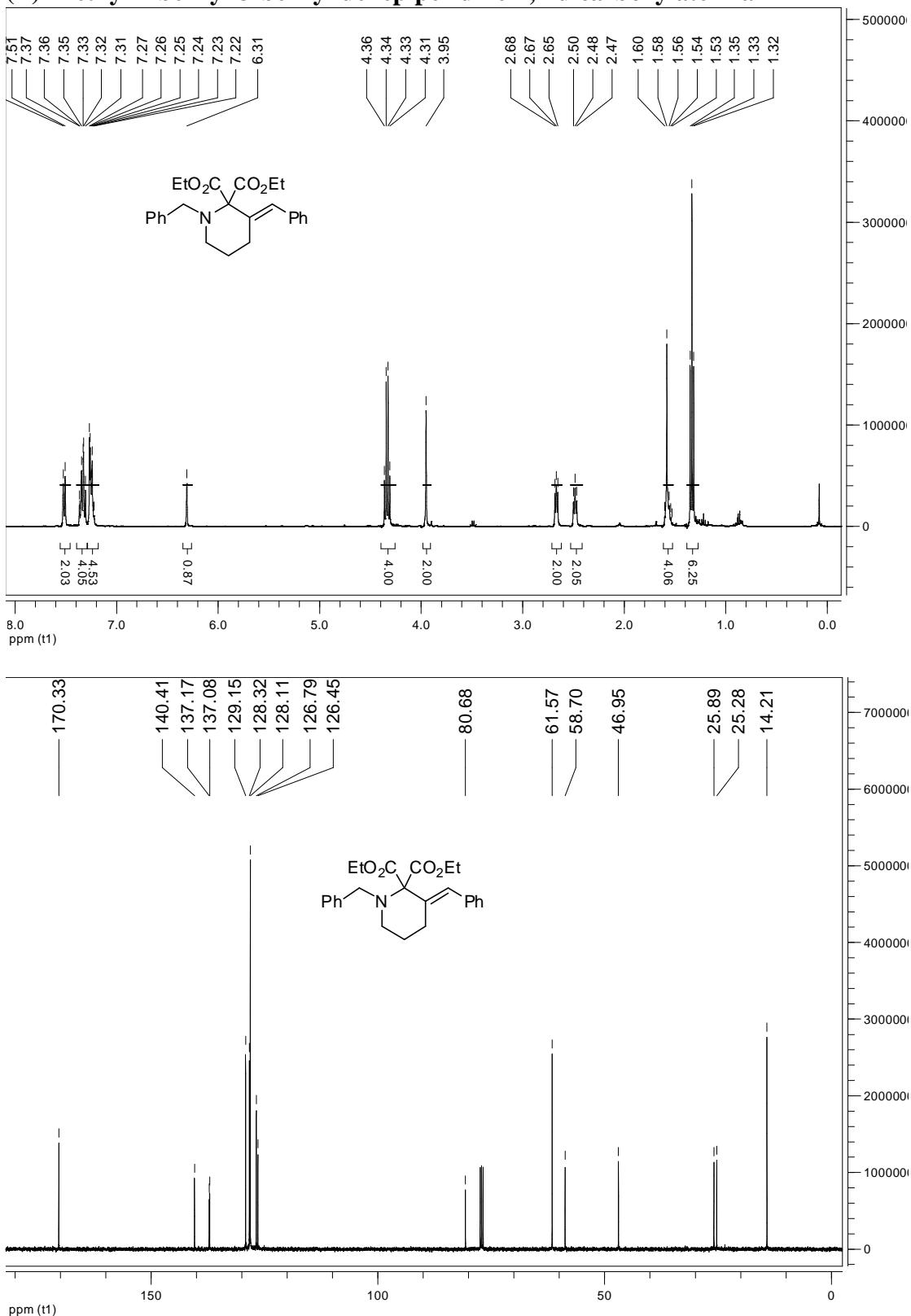
(E)-1-Benzyl 2,2-di-*tert*-butyl 3-benzylidenepyrrolidine-1,2,2-tricarboxylate 8f



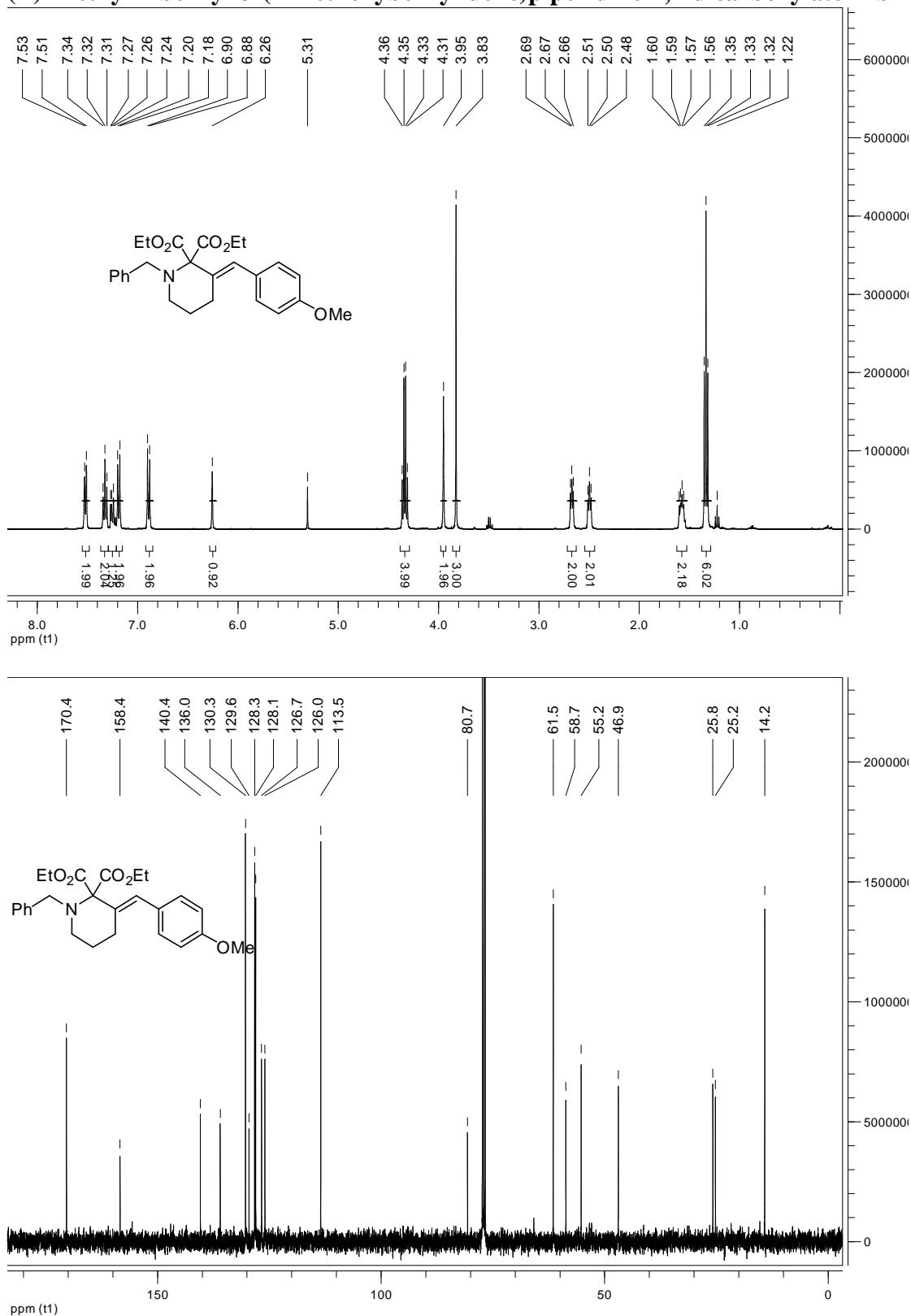
1-Benzyl 2,2-di-*tert*-butyl 3-methylenepyrrolidine-1,2,2-tricarboxylate 9f



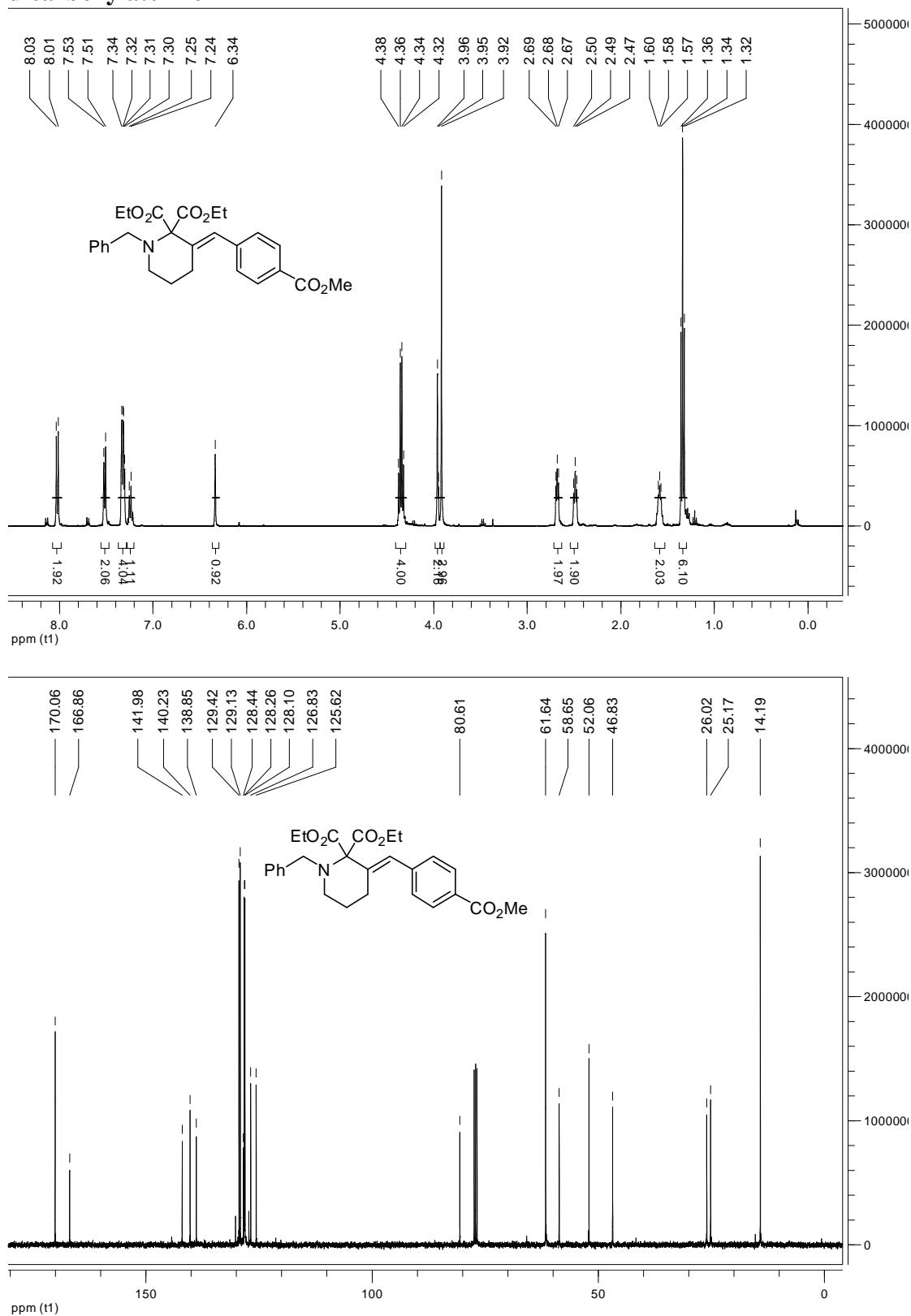
(E)-Diethyl 1-benzyl-3-benzylideneperidine-2,2-dicarboxylate 11a



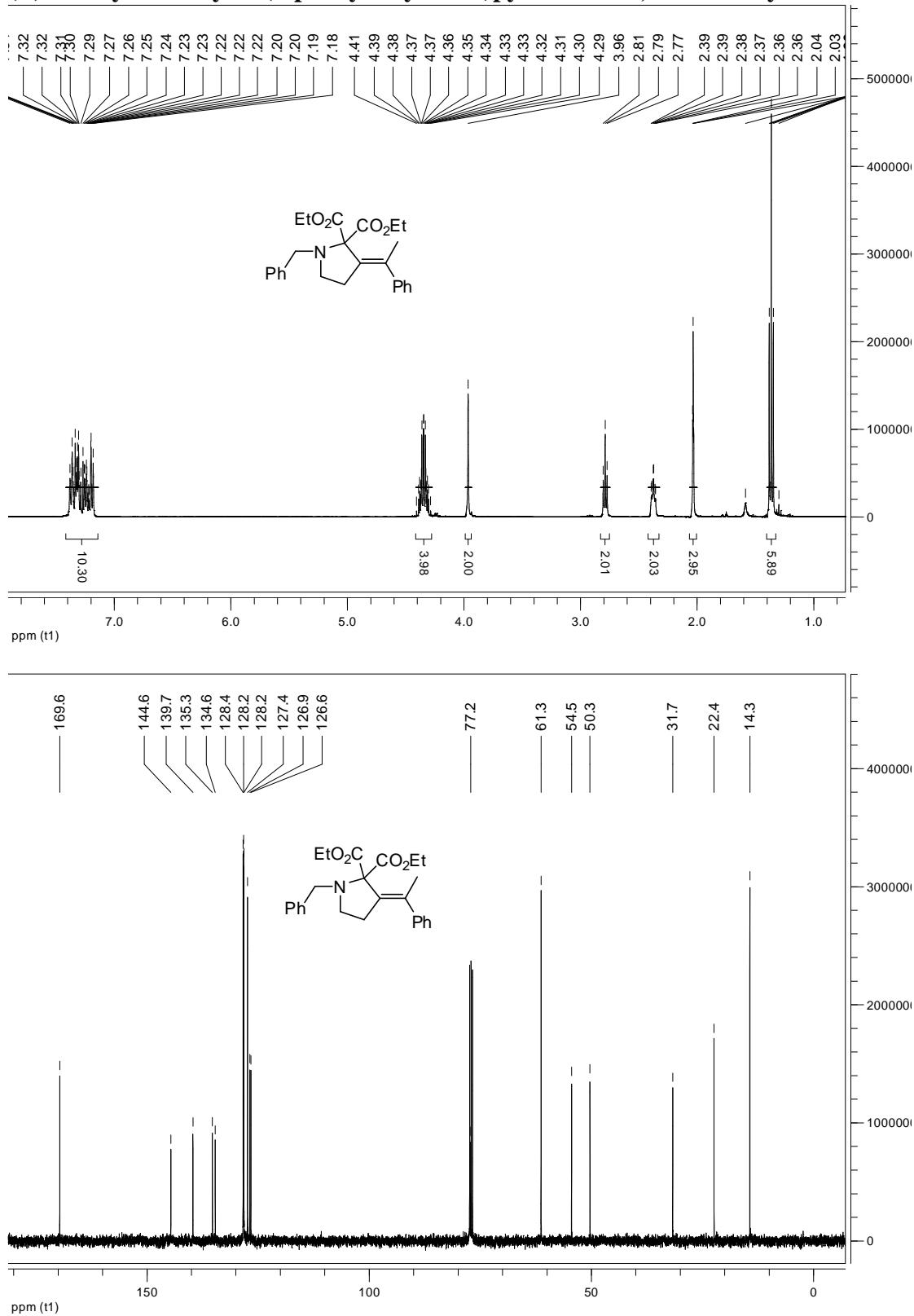
(E)-Diethyl 1-benzyl-3-(4-methoxybenzylidene)piperidine-2,2-dicarboxylate 11b



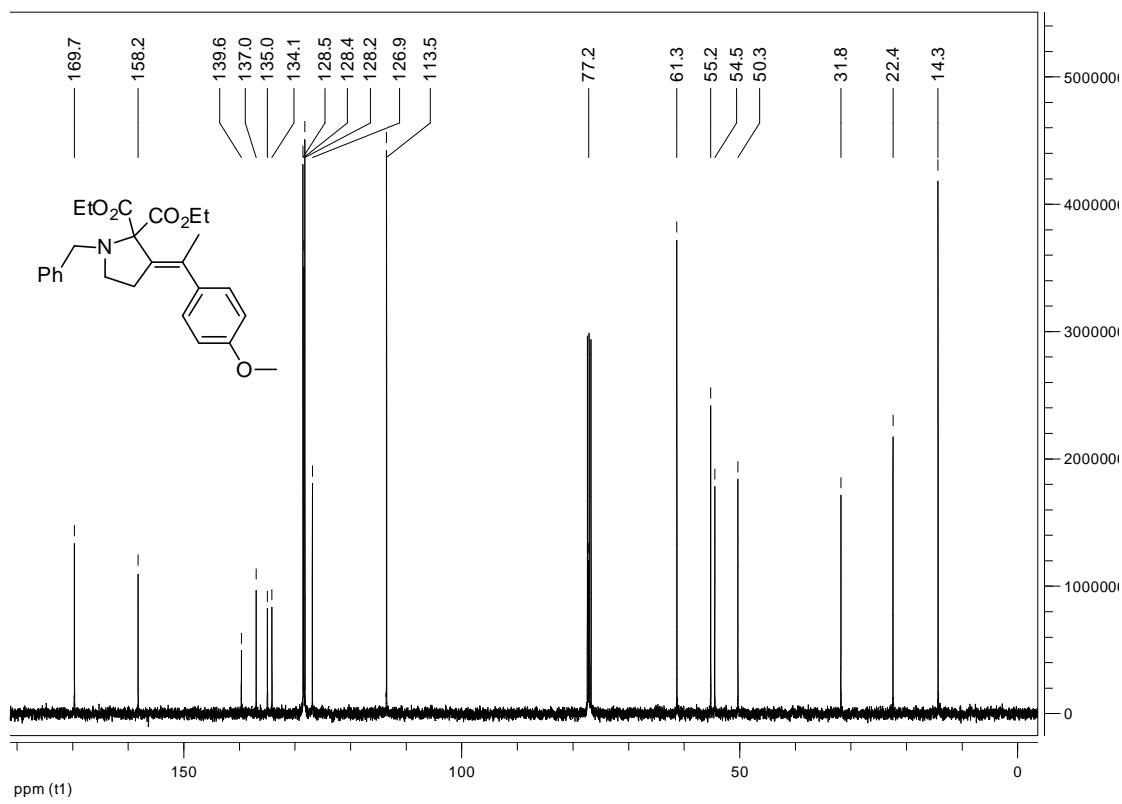
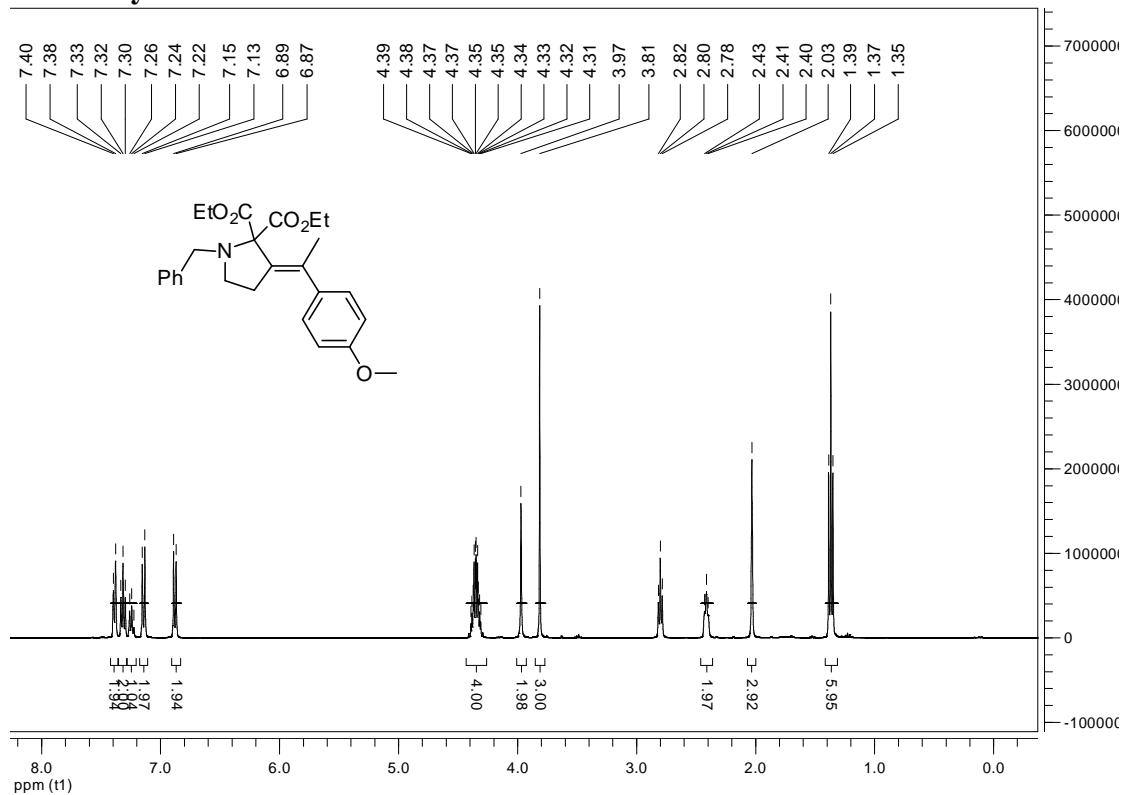
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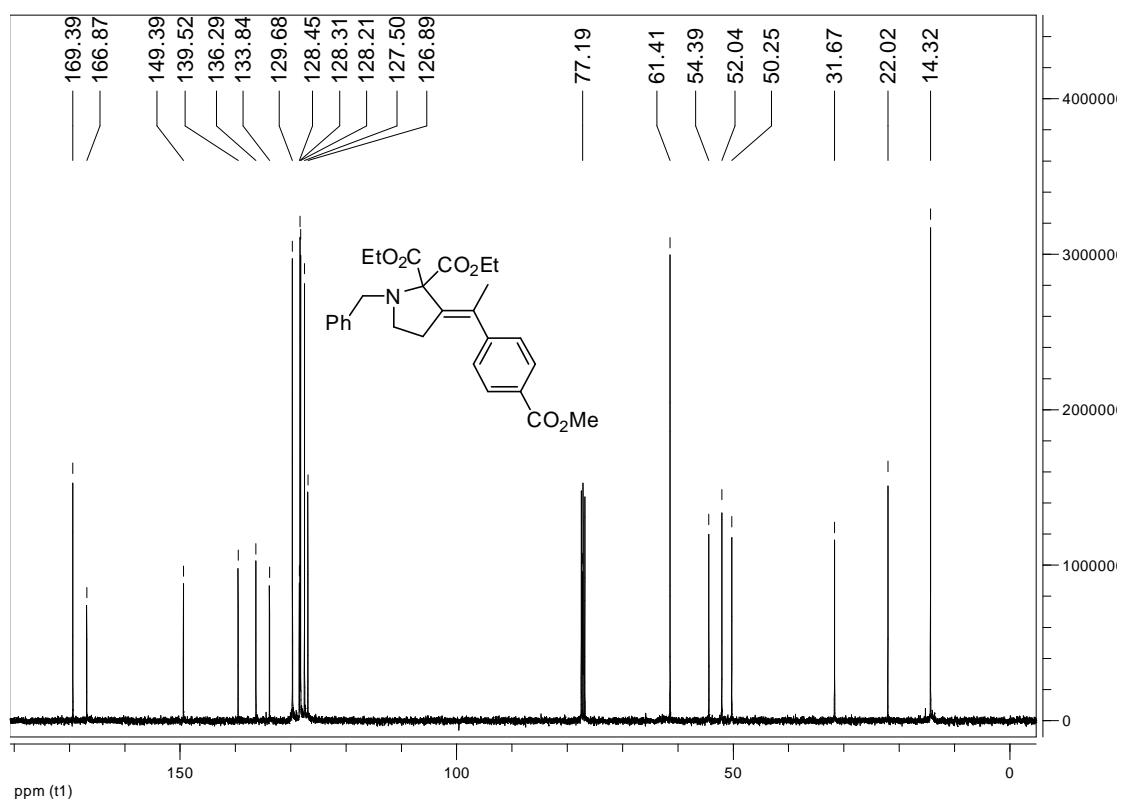
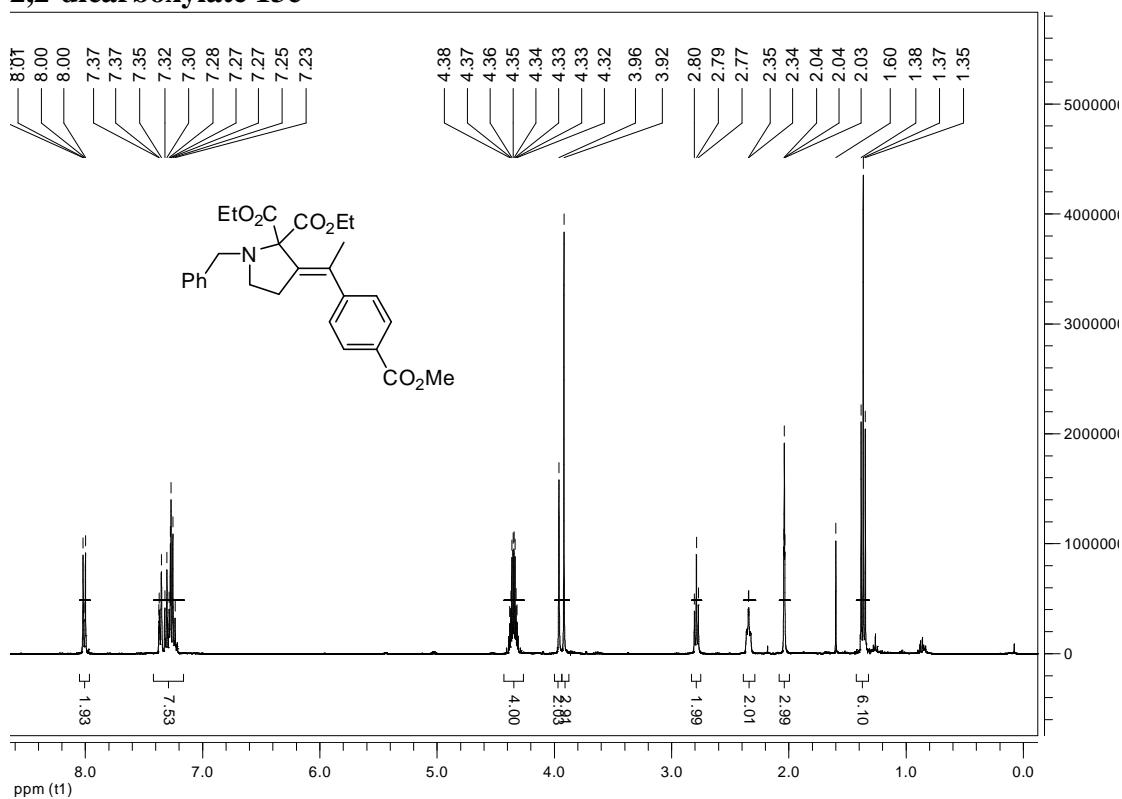
(*E*)-Diethyl 1-benzyl-3-(1-phenylethylidene)pyrrolidine-2,2-dicarboxylate 13a



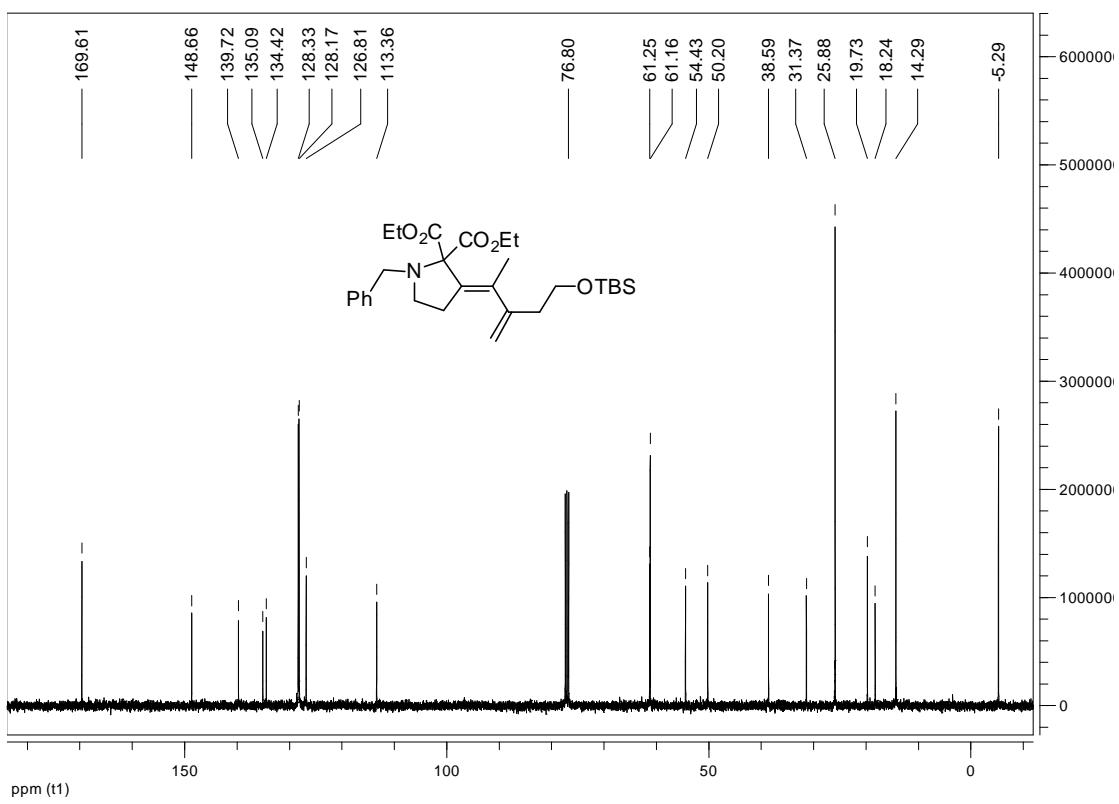
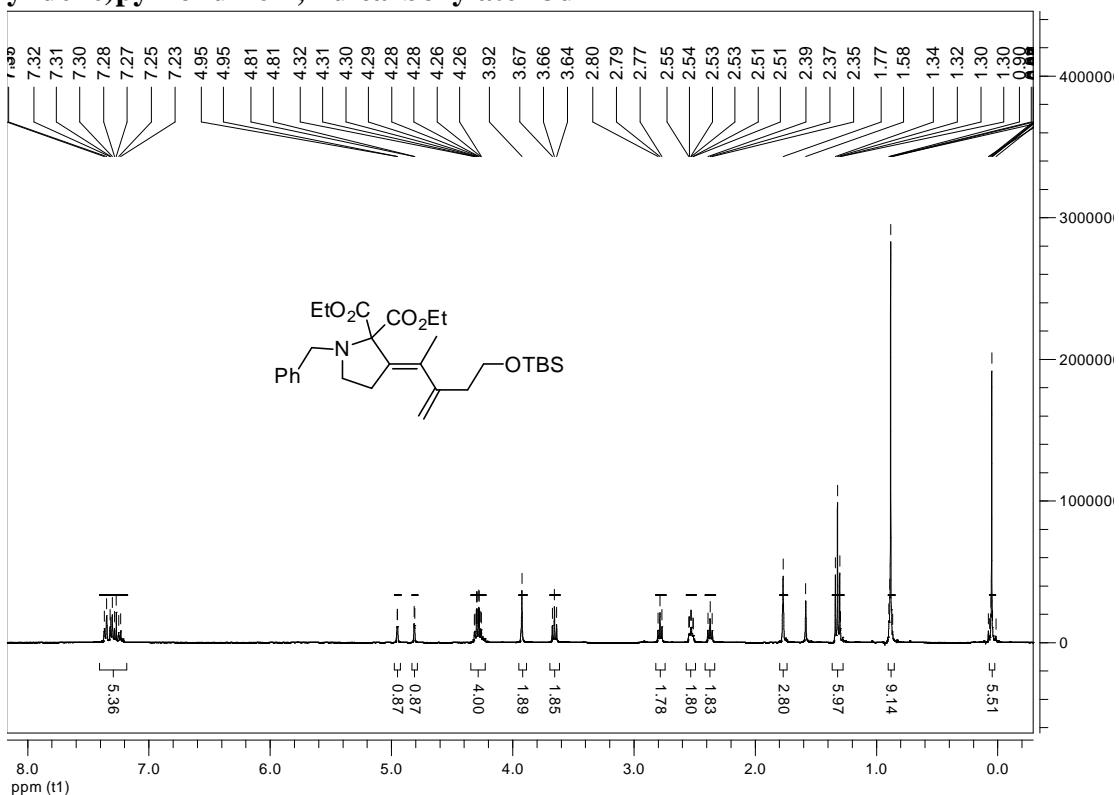
(E)-Diethyl 1-benzyl-3-(1-(4-methoxyphenyl)ethylidene)pyrrolidine-2,2-dicarboxylate 13b



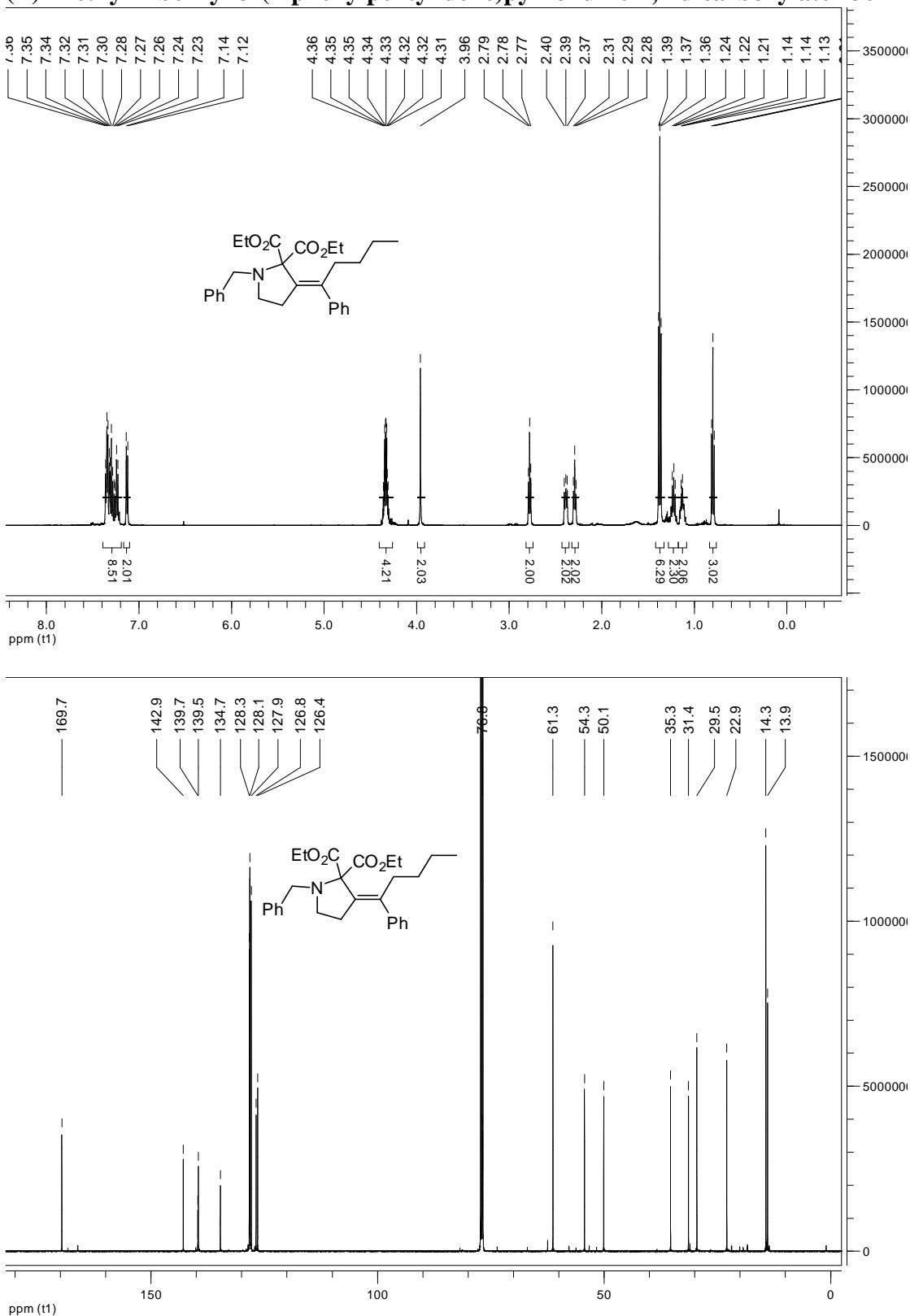
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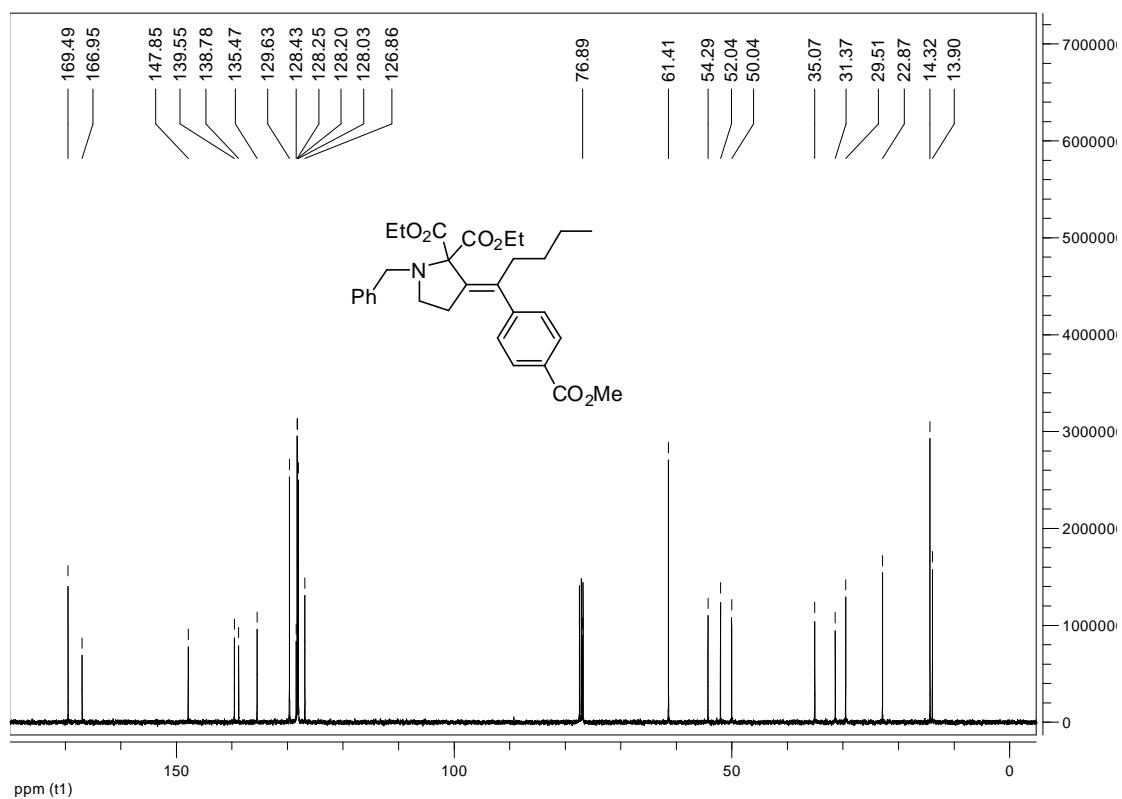
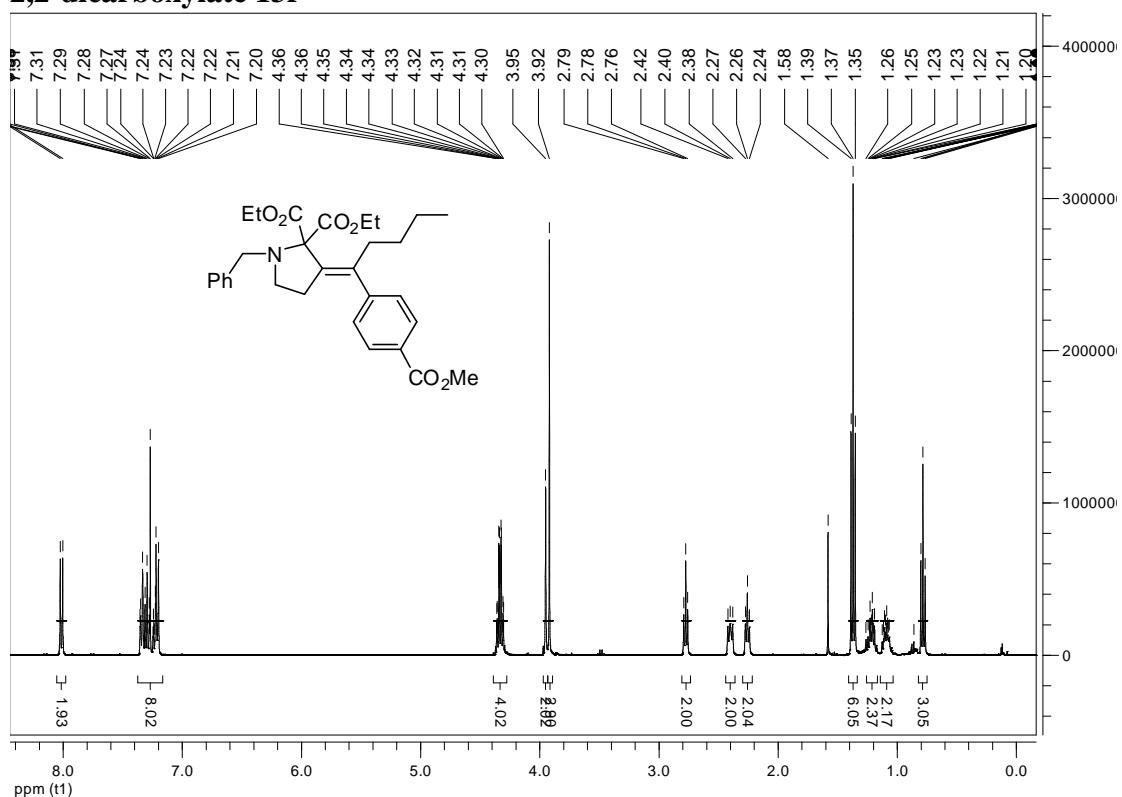
(E)-Diethyl 1-benzyl-3-(5-(tert-butyldimethylsilyloxy)-3-methylenepentan-2-ylidene)pyrrolidine-2,2-dicarboxylate 13d



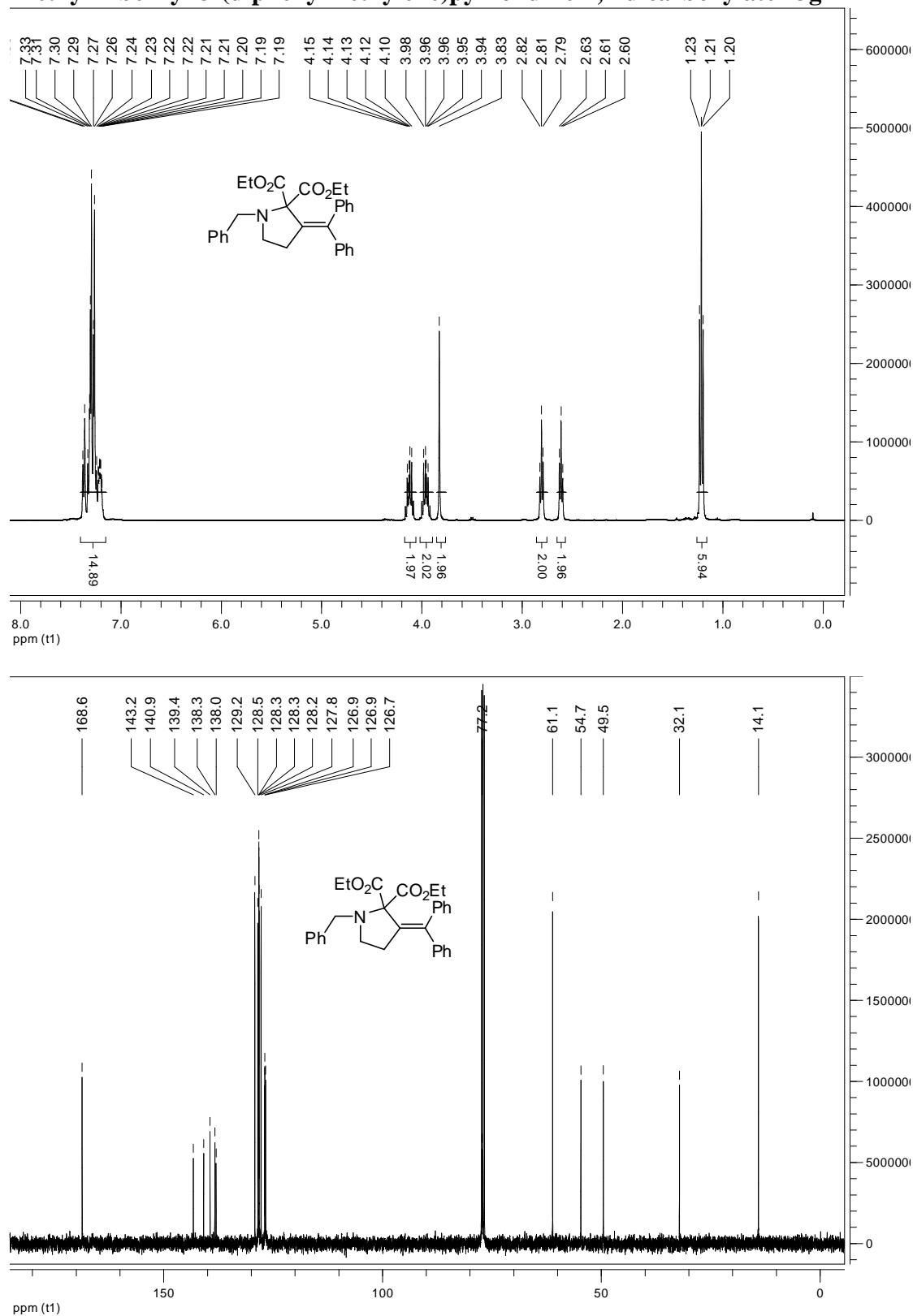
(E)-Diethyl 1-benzyl-3-(1-phenylpentylidene)pyrrolidine-2,2-dicarboxylate 13e



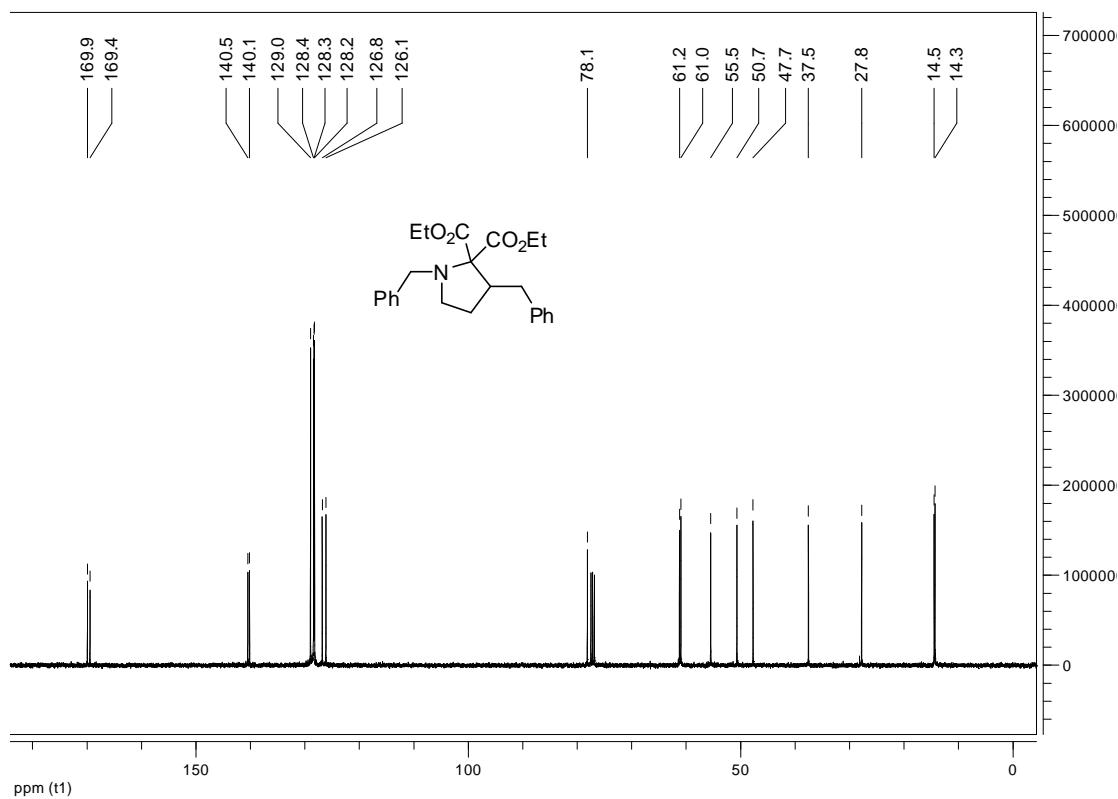
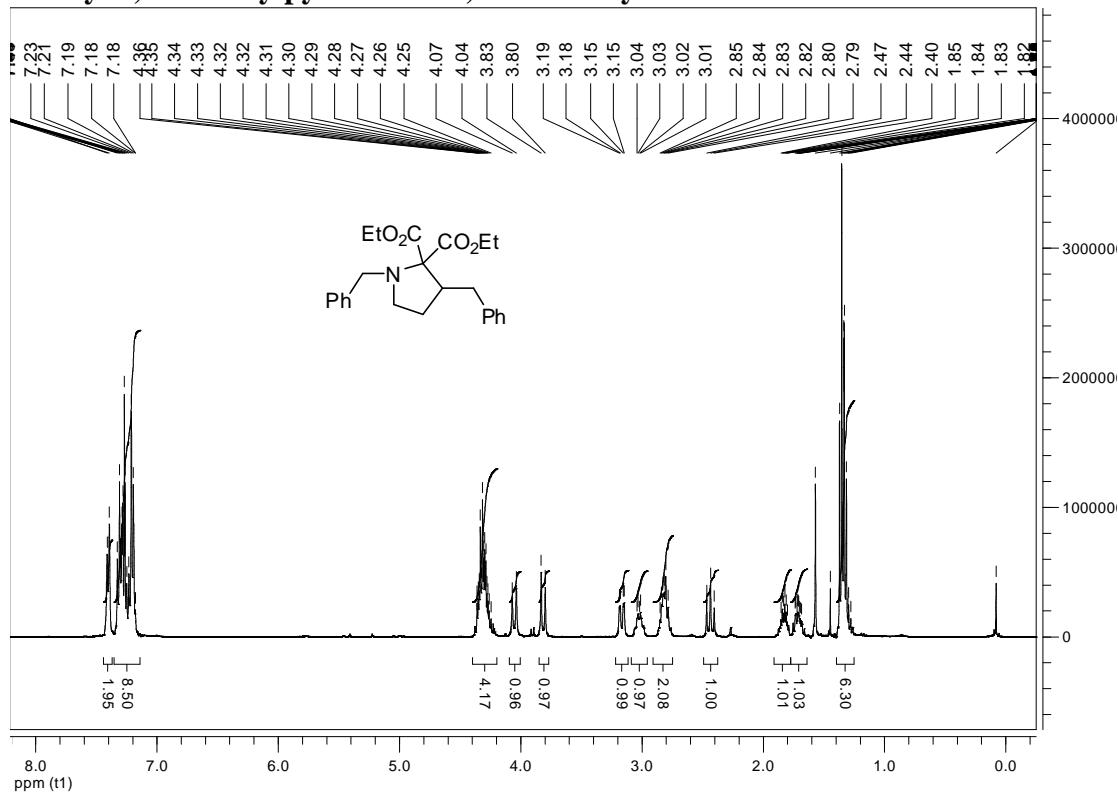
(E)-Diethyl 1-benzyl-3-(1-(4-(methoxycarbonyl)phenyl)pentylidene)pyrrolidine-2,2-dicarboxylate 13f



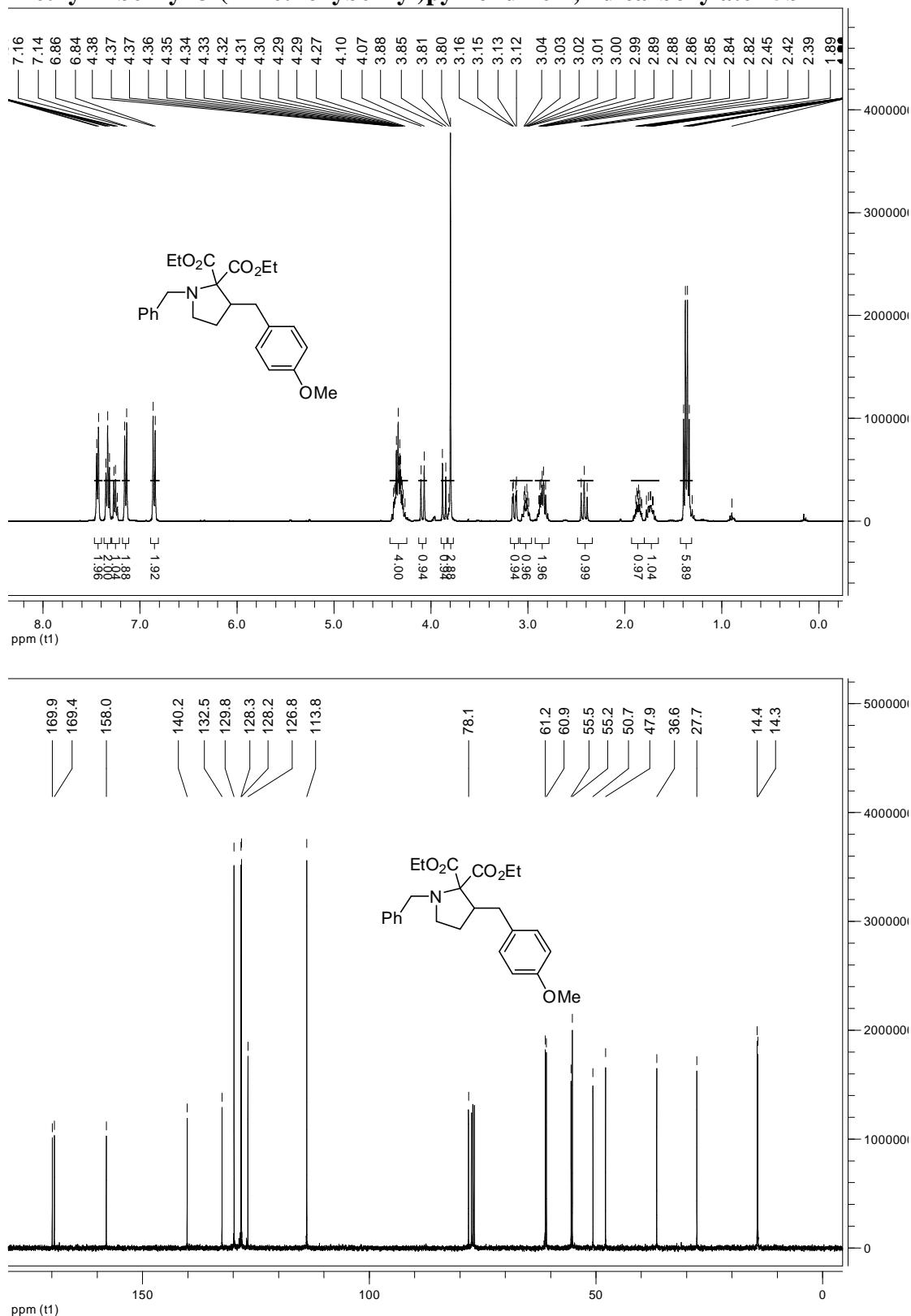
Diethyl 1-benzyl-3-(diphenylmethylene)pyrrolidine-2,2-dicarboxylate 13g



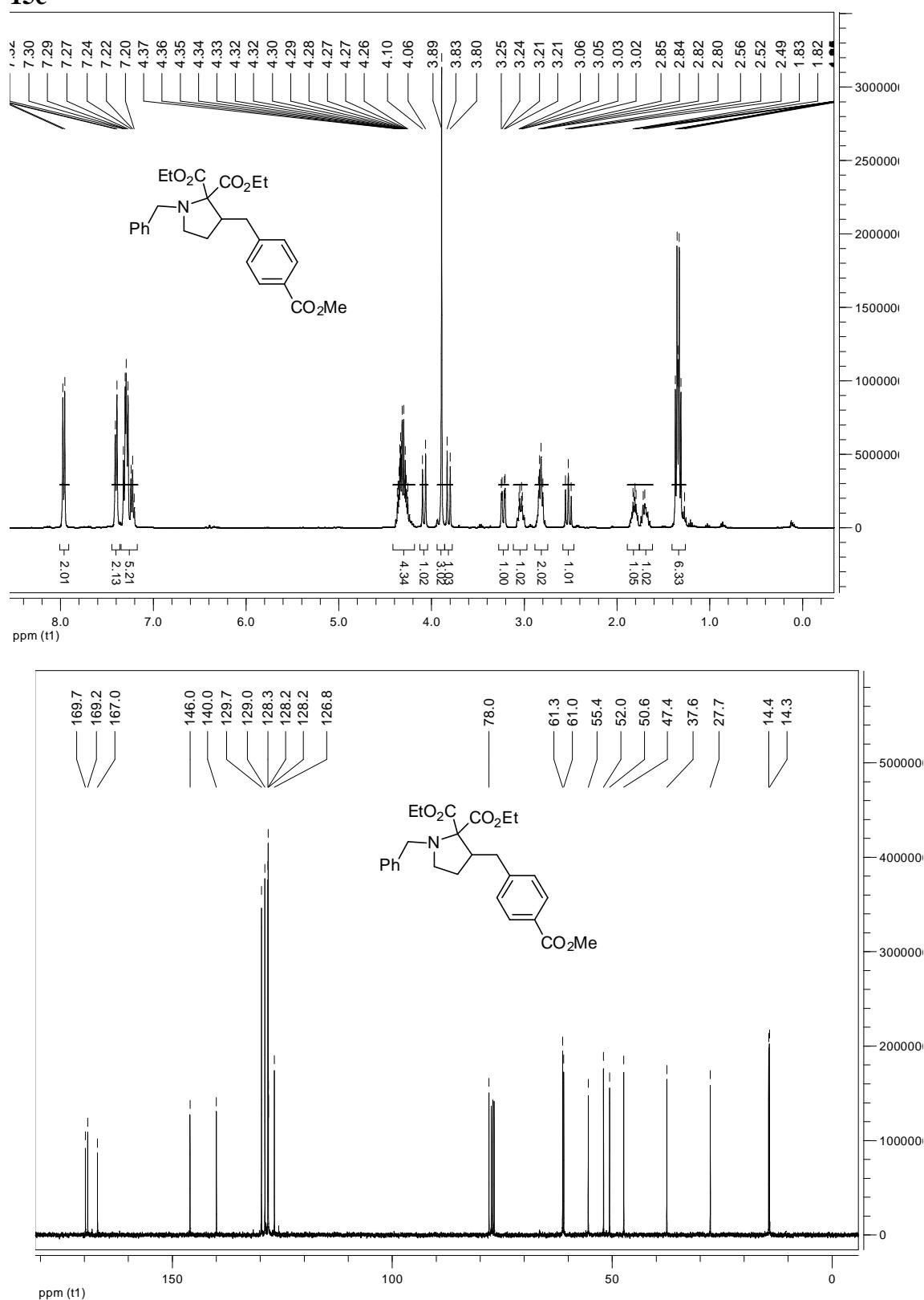
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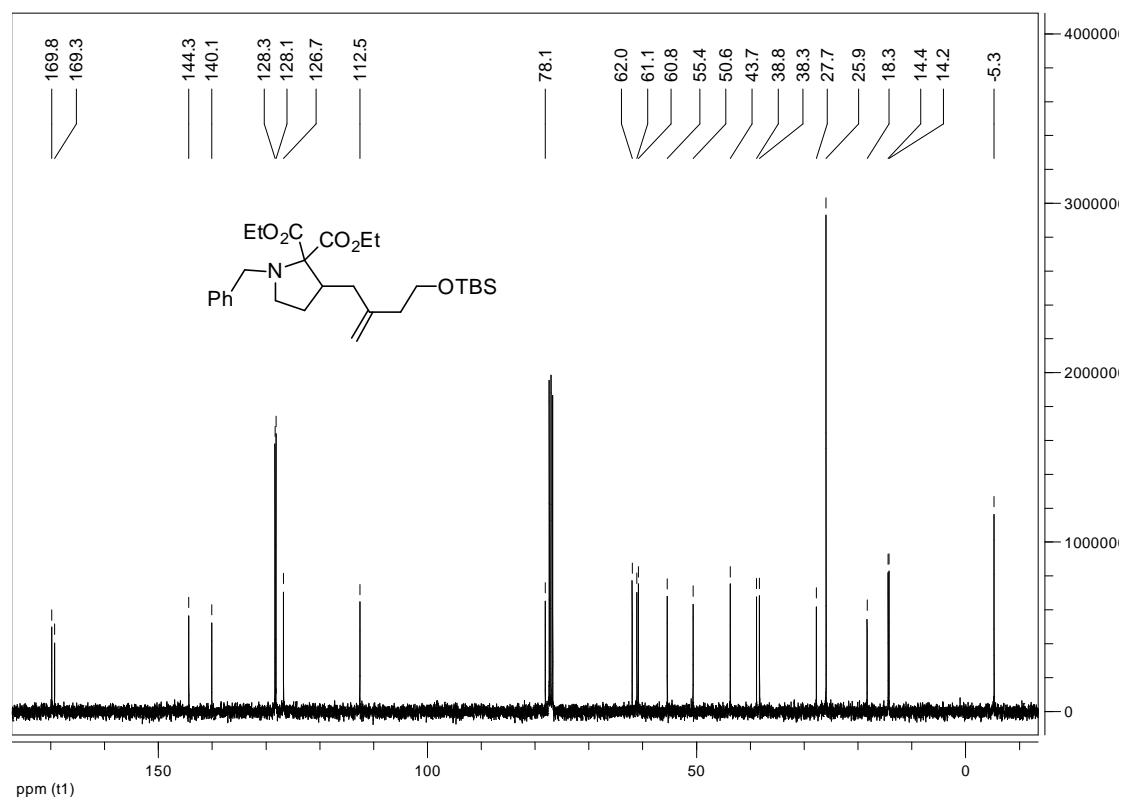
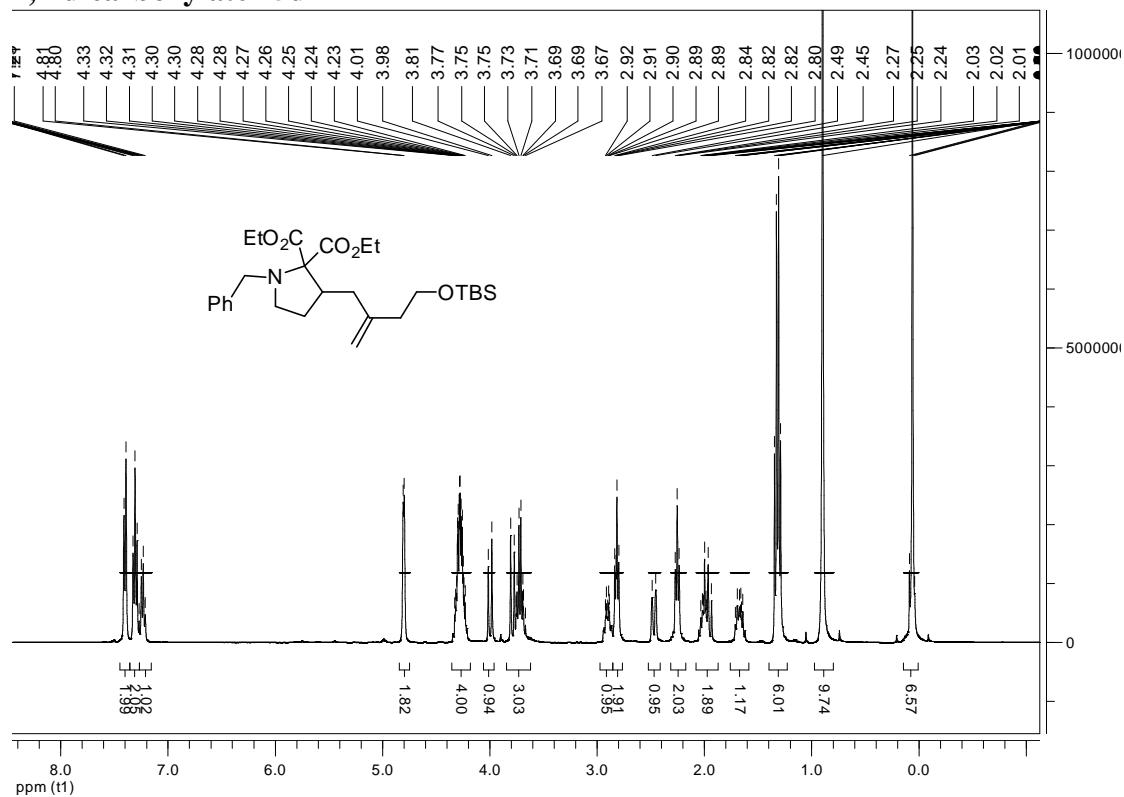
Diethyl 1-benzyl-3-(4-methoxybenzyl)pyrrolidine-2,2-dicarboxylate 15b



**Diethyl 1-benzyl-3-(4-(methoxycarbonyl)benzyl)pyrrolidine-2,2-dicarboxylate
15c**



Diethyl 1-benzyl-3-(4-(*tert*-butyldimethylsilyloxy)-2-methylenebutyl)pyrrolidine-2,2-dicarboxylate 15d



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