Manganese(III)-mediated radical cyclisations for the (*Z*)-selective synthesis of *exo*-alkylidene pyrrolidinones and pyrrolidines

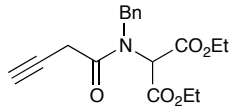
1. Introduction

^{1}H and ^{13}C 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 (δ=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. ^{13}C spectra were recorded with proton decoupling; HMQC, were recorded to assist assignment.
Infrared spectra were recorded on a 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 F_{254} silica gel and visualised by UV and aqueous potassium permanganate solution, ethanolic phosphomolybdic acid solution or ninhydrin in ethanol.
Solvents were purified by standard techniques. Petroleum ether (PE) refers to the fraction boiling at 40-60 °C.
Compounds **9a**, **10a** and **15a** have been previously reported.[1]

2. Synthesis of amido malonates

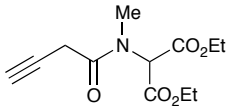
Based on the procedure of Hatakeyama:[2] carboxylic acid (1.2 eq.) was dissolved in DCM (1 mL/mmol malonate) and a few drops of dimethylformamide were added. Oxalyl chloride (1.1 eq.) was added and the reaction was allowed to stir at room temperature for 1 h. The solution of crude acid chloride was added dropwise to a solution of *N*-benzyldialkylamino malonate (1.0 eq.) in DCM (1.5 mL/mmol malonate) and saturated $NaHCO_3$ solution (1 mL/mmol malonate). The reaction was allowed to stir for 30 min at room temperature, the reaction mixture was then filtered through a silica pad, eluting with diethyl ether. The solvent was removed under reduced pressure to give the crude product.

Diethyl 2-(*N*-benzylbut-3-ynamido)malonate 7a



Butynoic acid (404 mg , 4.8 mmol, 1.2 eq.) and *N*-benzyl diethyl aminomalonate gave, after purification by FC (PE/Et_2O 1:1, R_f (Et_2O) = 0.65), diethyl 2-(*N*-benzylbut-3-ynamido)malonate **7a** (570.6 mg, 1.72 mmol, 43%) as a colorless oil together with a 2.2:1.0 mixture of a cyclised side product and the desired product **8a**:**7a** (318.3 mg combined, 0.96 mmol, 24%).
Approximately 9:1 mixture of rotamers at 400 MHz at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37-7.26 (*m*, 5H, H_{ar}), 5.43 (*s*, 1H, CH), 4.79 (*s*, 2H, CH_2Ar), 4.18-3.86 (*m*, 4H, 2xCH_2), 3.41 (*d*, 0.2H, *J* = 2.4 Hz, CH_2CON), 3.32 (*d*, 1.8H, *J* = 2.8 Hz, CH_2CON), 2.57 (*t*, 1H, *J* = 2.8 Hz, CCH), 2.23 (*t*, 1H, *J* = 2.8 Hz, CCH), 1.23-1.14 (*m*, 6H, 2xCH_3). Only the data for the major rotamer is given; the signals of the minor rotamer are not well resolved:^{13}C-NMR (100 MHz, $CDCl_3$): 168.3 (CO), 165.9 (CO), 135.8 (C_{ar}), 128.8 (2xCH_{ar}), 127.8 (CH_{ar}), 126.4 (2xCH_{ar}), 75.7 (C_{sp}), 72.7 (CH_{sp}), 62.2 (2xCH_2), 61.3 (CH), 51.3 (CH_2), 26.1 (CH_2), 13.9 (2xCH_3). IR (film): 3282m, 2981m, 2929m, 1739s, 1672m, 1496w, 1432w, 1389w, 1368w, 1298w, 1260w, 1179m, 1029m, 669w. MS (ESI+): 332.16 (25, $[M+H]^+$), 354.14 (45,$[M+Na]^+$), 390.19 (79), 434.25 (82), 685 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{18}H_{21}NNaO_5$ ($[M+Na]^+$) 354.1312, found 354.1310.

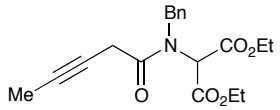
Diethyl 2-(*N*-methylbut-3-ynamido)malonate 7b



Butynoic acid (807 mg, 9.6 mmol, 1.2 eq.) and *N*-methyl diethyl aminomalonate (1.52 g, 8.0 mmol, 1.0 eq.) gave, after purification by FC (PE/Et_2O 1:2), diethyl 2-(*N*-methylbut-3-ynamido)malonate **7b** (1.286 g, 5.04 mmol, 63%) as a colorless oil.

The product is a 30:1 mixture of rotamers at room temperature. The analytical data is only given for the major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): 5.93 (s, 1H, CH), 4.27 (*q*, 4H, *J* = 7.0 Hz, 2xCH_2O), 3.40 (*d*, 2H, *J* = 2.8 Hz, CH_2CO), 3.19 (*s*, 3H, CH_3N), 2.25 (*t*, 1H, *J* = 2.8 Hz, CCH), 1.31 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.4 (CO), 166.5 (2xCO), 76.4 (C_{sp}), 72.5 (CH_{sp}), 61.9 (2xCH_2), 60.5 (CH) , 33.5 (CH_3), 25.7 (CH_2), 13.8 (2xCH_3). IR (film): 3280m, 2984m, 1739s, 1668s, 1471w, 1447w, 1392w, 1370w, 1181m, 1114w, 1035m. MS (ESI-): 254.09 (80, $[M-H]^-$), 390.08 (64), 531.17 (100, $[2M-2H+Na]^-$). HRMS (ESI): calculated for $C_{12}H_{18}NO_5$ ($[M+H]^+$) 256.1179, found 256.1170.

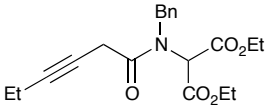
Diethyl 2-(*N*-benzylpent-3-ynamido)malonate 9a



Pent-3-ynoic acid (374 mg, 3.80 mmol, 1.2 eq.) and diethyl 2-(benzylamino)malonate (840 µL 3.17 mmol, 1.0 eq.) gave, after purification by FC (PE/EtOAc 1:1 (R_f (PE/EtOAc 1:1) = 0.25), diethyl 2-(*N*-benzylpent-3-ynamido)malonate **9a** (968 mg, 2.80 mmol, 88%) as a yellow oil.

The product is a 7:1 mixture of rotamers at room temperature. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37-7.19 (*m*, 5H, H_{ar}), 5.38 and 5.36 (*s*, 1H, CHN), 4.80 (*s*, 2H, CH_2Ph), 4.20-4.01 and 3.92-3.84 (*m*, 4H, 2xCH_2O), 3.36 and 3.28 (*q*, 2H, *J* = 2.5 Hz, CH_2CO), 1.81 and 1.77 (*t*, 3H, *J* = 2.6 Hz, CH_3CC), 1.21 and 1.16 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). The NMR showed a mixture of rotamers, only the data for the major one is given. ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4 (CO), 165.9 (2xCO), 136.0 (C_{ar}), 128.6 (2xCH_{ar}), 127.6 (CH_{ar}), 126.5 (2xCH_{ar}), 80.1 (C_{sp}), 70.5 (C_{sp}), 62.0 (2xCH_2), 61.3 (CH), 51.3 (CH_2), 26.3 (CH_2), 13.8 (2xCH_3), 3.6 (CH_3). IR (film): 3064w, 3030w, 2982m, 2922w, 1740s, 1672s, 1496w, 1442m, 1369m, 1299m, 1252m, 1179s, 1096w, 1029m, 975w, 736m, 701m. MS (ESI+): 346.19 (17, $[M+H]^+$), 368.15 (63, $[M+Na]^+$), 447.26 (100), 713.23 (99, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{19}H_{23}NaNO_5$ ($[M+H]^+$), 368.1468 found 368.1465.

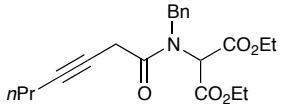
Diethyl 2-(*N*-benzylhex-3-ynamido)malonate 9b



Hex-3-ynoic acid (542 mg, 4.84 mmol) and diethyl 2-(benzylamino)malonate (512 mg, 1.93 mmol) gave, after purification by FC (PE/Et_2O 1:1), the title **9b** compound as a colourless oil (394 mg, 1.09 mmol, 57%). R_f = 0.31 (PE/Et_2O 1:1).

Approximately 2:1 mixture of rotamers at room temperature, only the major rotamer is completely assigned. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34-7.17 (*m*, 5H, H_{ar}), 5.39 & 5.34 (*s*, 1H, CH), 4.79 (*s*, 2H, CH_2Ph), 4.17-3.82 (*m*, 4H, 2xCH_2O), 3.35 /3.28 (*s*, 2H, CH_2CO), 2.12 (*q*, 2H, *J* = 7.2 Hz, CH_3CH_2CC), 1.19/1.13 (*t*, 6H, *J* = 7.2 Hz, C*H*$_3$$CH_2O$), 1.06 (*t*, 3H, *J* = 7.5 Hz, C*H*$_3$$CH_2CC$). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4 (2xCO), 165.9 (CO), 136.0 (C_{ar}), 128.6 (2xCH_{ar}), 127.7 (CH_{ar}), 126.6 (2xCH_{ar}), 86.1 (C_{sp}), 70.7 (C_{sp}), 62.3 (CH), 61.3 (2xCH_2), 51.3 (CH_2), 26.4 (CH_2), 13.8 (2xCH_3), 13.7 (CH_3) 12.4 (CH_2). IR (film): 3064m, 3031m, 2981s, 2939s, 2879m, 2249w (C≡C), 1742s (C=O, ester), 1672s (C=O, amide). MS (ESI+): 360.2 (62, $[M+H]^+$), 382.2 (80, $[M+Na]^+$), 741.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{20}H_{25}NNaO_5$ ($[M+Na]^+$) 382.1625, found 382.1622.

Diethyl 2-(*N*-benzylhept-3-ynamido)malonate 9c

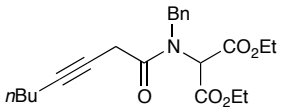


Hept-3-ynoic acid (349 mg, 2.76 mmol) and diethyl 2-(benzylamino)malonate (610 mg, 2.30 mmol) gave, after purification by FC (PE/Et_2O 1:1) the title compound **9c** as a colourless oil (553 mg, 1.29 mmol, 56%). R_f = 0.30 (PE/Et_2O 1:1).

Approximately 7:1 mixture of rotamers at room temperature, only the major rotamer is completely assigned. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34-7.17 (*m*, 5H, H_{ar}), 5.41/5.35 (*s*, 1H, CH), 4.80 (*s*, 2H, CH_2Ph), 4.17-3.84 (*m*, 4H, 2xCH_2O), 3.36/3.29 (*s*, 2H, CH_2CO), 2.12-2.09 (m, 2H, $CH_3CH_2CH_2$), 1.47 (*tt*, 2H, *J* = 7.1, 7.1 Hz, $CH_3CH_2CH_2$) 1.19/1.13 (*t*, 6H, *J* = 7.1 Hz, OCH_2CH_3), 1.06 (*t*, 3H, *J* = 7.1 Hz, $CH_3CH_2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4 (2xCO), 165.9 (CO), 136.0 (C_{ar}), 128.6 (2xCH_{ar}), 128.0 (CH_{ar}), 126.9 (2xCH_{ar}), 84.7 (C_{sp}), 71.4 (C_{sp}), 62.0 (CH), 61.2 (CH_2), 51.3 (CH_2), 26.5 (CH_2), 22.0 (CH_2), 20.8CH_2), 13.8 (2xCH_3), 13.4

(CH_3). IR (film): 3064m, 3031m, 2907m, 2874m, 2965s, 2936s, 2874m, 2242w (C≡C), 1742s (C=O, ester), 1674s (C=O, amide). MS (ESI+): 374.2 (55, $[M+H]^+$), 396.2 (72, $[M+Na]^+$), 369.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{21}H_{27}NNaO_5$ ($[M+Na]^+$) 396.1781, found 396.1781.

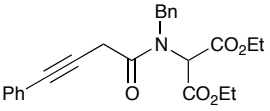
Diethyl 2-(N-benzyloct-3-ynamido)malonate 9d



Oct-3-ynoic acid (590 mg, 4.21 mmol), prepared according to method of Alsters,[3] and diethyl 2-(benzylamino)malonate (928 mg, 3.50 mmol) gave, after purification by FC (PE/Et_2O 1:1) the title compound **9d** as a colourless oil (1.12 g, 2.89 mmol, 83%). R_f = 0.31 (PE/Et_2O 1:1).

Approximately 1:5 mixture of rotamers at 400 MHz at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37-7.23 (*m*, 5H, H_{ar}), 5.37 (*s*, 1H, CH), 4.82 (*s*, 2H, CH_2Ph), 4.20-4.10 (*m*, 2H, OCH_2), 4.10-4.00 (*m*, 2H, OCH_2), 3.31 (*t*, 2H, *J* = 2.3 Hz, CH_2CO), 2.14 (*tt*, 2H, *J* = 7.0, 2.3 Hz, $CH_3CH_2CH_2CH_2$), 1.30-1.51 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 1.22 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3), 0.88 (*t*, 3H, *J* = 7.1 Hz, $CH_3CH_2CH_2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4 (CO), 165.9 (2xCO), 136.0 (C_{ar}), 128.7 (2xCH_{ar}), 127.7 (CH_{ar}), 126.6 (CH_{ar}), 84.9 (C_{sp}), 71.2 (C_{sp}), 62.1 (CH_2), 61.2 (CH), 51.3 (CH_2), 30.7 (CH_2), 26.5 (CH_2), 21.9 (CH_2), 18.4 (CH_2), 13.9 (2xCH_3), 13.6 (CH_3). IR (film): 2959m, 2934m, 2870w, 1741s (C=O, ester), 1672s (C=O, amide). MS (ESI+): 388.21 (19, $[M+H]^+$), 410.18 (78, $[M+Na]^+$), 797.29 (100, $[2M+Na]^+$). HRMS (FI): calculated for $C_{22}H_{29}NO_5$ ($[M]^+$) 387.2046, found 387.2007.

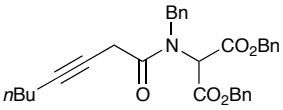
Diethyl 2-(*N*-benzyl-4-phenylbut-3-ynamido)malonate 9e



4-Phenylbut-3-ynoic acid (564 mg, 3.53 mmol) and diethyl 2-(benzylamino)malonate (903 mg, 2.94 mmol) gave, after purification by FC (PE/Et_2O 1:1), the title compound **9e** as a colourless oil (723 mg, 1.77 mmol, 60%). R_f = 0.31 (PE/Et_2O 1:1).

Approximately 6:1 mixture of rotamers at room temperature. Only the major rotamer is assigned. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.42-7.20 (*m*, 10H, H_{ar}), 5.39 (*s*, 1H, CH), 4.88 (*s*, 2H, CH_2Ph), 4.24-4.13 (*m*, 2H, CH_2O), 4.13-4.04 (*m*, 2H, CH_2O), 3.57 (*s*, 2H, CH_2CO), 1.22 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.7 (2xCO), 165.9 (CO), 135.9 (C_{ar}), 131.7 (2xCH_{ar}), 128.8 (2xCH_{ar}), 128.2 (3xCH_{ar}), 127.8 (CH_{ar}), 126.6 (2xCH_{ar}), 122.9 (C_{ar}), 84.4 (C_{sp}), 81.1 (C_{sp}), 62.4 (2xCH_2O), 61.4 (CH), 51.5 (CH_2), 27.2 (CH_2), 13.6 (2xCH_3). IR (film): 2983w, 2938w, 1739s (C=O, ester), 1672s (C=O, amide). MS (ESI+): 408.2 (73, $[M+H]^+$), 430.2 (53, $[M+Na]^+$), 837.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{24}H_{25}NNaO_5$ ($[M+Na]^+$) 430.1625, found 430.1624.

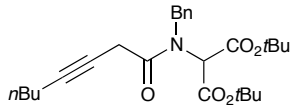
Dibenzyl 2-(*N*-benzyloct-3-ynamido)malonate 11



Oct-3-ynoic acid (300 mg, 2.14 mmol), Oct-3-ynoic acid (590 mg, 4.21 mmol), prepared according to method of Alsters,[3], and dibenzyl 2-(benzylamino)-malonate (701 mg, approx. 1.80 mmol) gave, after purification by FC (PE/Et_2O 1:1), the title compound **11** as a colourless oil (299 mg, 0.60 mmol, 33%). R_f = 0.29 (PE/Et_2O 1:1).

Approximately 6:1 mixture of rotamers at room temperature, only the major rotamer is assigned: ^{1}H-NMR (400 MHz, $CDCl_3$): 7.39-7.26 (*m*, 15H, H_{ar}), 5.29 (*s*, 1H, CH), 5.10 (*d*, 2H, *J* = 12.2 Hz, 2xC*H*HPh), 5.03 (*s*, 2H, *J* = 12.2 Hz, 2xCH*H*Ph), 4.79 (*s*, 2H, NCH_2Ph), 3.32 (*t*, 2H, *J* = 2.3 Hz, CH_2CO), 2.10 (*tt*, 2H, *J* = 7.0, 2.3 Hz, $CH_3CH_2CH_2CH_2$), 1.44-1.26 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 0.86 (*t*, 3H, *J* = 7.1 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.4 (CO), 165.6 (2xCO), 135.7 (C_{ar}), 134.9 (2xC_{ar}), 128.8 (2xCH_{ar}), 128.5 (4xCH_{ar}), 128.3 (2xCH_{ar}), 128.1 (4xCH_{ar}), 127.7 (CH_{ar}), 126.9 (2xCH_{ar}), 85.0 (C_{sp}), 71.3 (C_{sp}), 67.8 (CH), 51.8 (CH_2), 30.7 (CH_2), 26.6 (CH_2), 22.0 (CH_2), 18.5 (CH_2), 13.6 (CH_3). IR (film): 3063w, 3032w, 2957m, 2932m, 2859w, 2361m (C≡C), 2341m, 1743s (C=O, ester), 1672s (C=O, amide). MS (ESI+): 534.2 (100, $[M+Na]^+$). HRMS (ESI): calculated for $C_{32}H_{33}NNaO_5$ ($[M+Na]^+$) 534.2251, found 534.2259.

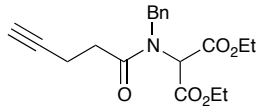
Di-*tert*-butyl 2-(*N*-benzyloct-3-ynamido)malonate 13



Oct-3-ynoic acid (590 mg, 4.21 mmol), prepared according to method of Alsters,[3] and di-*tert*-butyl 2-(benzylamino)malonate (1.08 g, 3.50 mmol), gave, after purification by FC (PE/Et_2O 2:1), the title compound **13** as a colourless oil (1.42 g, 3.30 mmol, 94%). R_f = 0.33 (PE/Et_2O 2:1).

Approximately 7:1 mixture of rotamers at room temperature, only the major rotamer is assigned: ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38-7.18 (*m*, 5H, H_{ar}), 5.37 (*s*, 1H, CH), 4.82 (*s*, 2H, CH_2Ph), 3.24 (*t*, 2H, *J* = 2.4 Hz, CH_2CO), 2.14 (*tt*, 2H, *J* = 7.0, 2.4 Hz, $CH_3CH_2CH_2CH_2$), 1.47-1.30 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 1.38 (*s*, 18H, 2x$C(CH_3)_3$), 0.88 (*t*, 3H, *J* = 7.2 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.5 (CO), 165.1 (2xCO), 136.7 (C_{ar}), 128.7 (2xCH_{ar}), 127.4 (CH_{ar}), 126.3 (2xCH_{ar}), 84.6 (C_{sp}), 82.9 (2xC), 71.5 (C_{sp}), 62.8 (CH), 50.8 (CH_2), 30.7 (CH_2), 27.7 (6xCH_3), 26.5 (CH_2), 21.9 (CH_2), 18.5 (CH_2), 13.6 (CH_3). IR (film): 2977m, 2933m, 2871m, 2361w, 2341w (C-C), 1735s (C=O, ester), 1674s (C=O, amide). MS(ESI+): 444.30 (20, $[M+H]^+$), 466.25 (74, $[M+Na]^+$), 904.50 (100). HRMS (FI): calculated for $C_{26}H_{37}NO_5$ ($[M]^+$) 443.2672, found 443.2674.

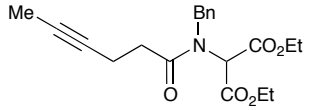
Diethyl 2-(*N*-benzylpent-4-ynamido)malonate 17a



Pentynoic acid (197 mg, 2.00 mmol) and diethyl 2-benzylamino)malonate (512 mg, 1.67 mmol) gave, after purification by FC (PE/Et_2O 1:1), the title compound **17a** as a colourless oil (585 mg, 1.51 mmol, 90%). R_f = 0.29 (PE/Et_2O 1:1).

Approximately 12:1 mixture of rotamers at room temperature, only the major rotamer is assigned: ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37-7.19 (*m*, 5H, H_{ar}), 5.53 (*s*, 1H, CH), 4.75 (*s*, 2H, CH_2Ph), 4.07-3.99 (*m*, 2H, 2xOC*H*H), 4.17-4.09 (*m*, 2H, 2xCH*H*O), 2.65-2.62 (*m*, 2H, CH_2CO), 2.57-2.53 (*m*, 2H, $CCCH_2$), 1.95 (*t*, 1H, *J* = 2.4 Hz, CCH), 1.20 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.6 (CO), 165.2 (2xCO), 136.1 (C_{ar}), 128.7 (2xCH_{ar}), 127.6 (CH_{ar}), 126.2 (2xCH_{ar}), 83.0 (C_{sp}), 68.9 (C_{sp}), 62.1 (2xCH_2), 61.0 (CH), 50.6 (CH_2), 32.4 (CH_2), 14.3 (CH_2), 13.8 (2xCH_3). IR (film): 3286m (C≡C-H), 2983m, 2938w, 2360w (C-C), 1739s (C=O, ester), 1664s (C=O amide). MS (ESI+): 346.2 (60, $[M+H]^+$), 363.2 (89, $[M+NH_4]^+$), 368.2 (24, $[M+Na]^+$), 713.2 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{19}H_{23}NNaO_5$ ($[M+Na]^+$) 368.1468, found 368.1468.

Diethyl 2-(*N*-benzylhex-4-ynamido)malonate 17b

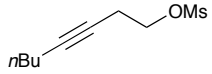


Hex-4-ynoic acid (contaminated with sorbic acid) (154 mg, 1.38 mmol) and diethyl 2-(benzylamino)malonate (305 mg, 1.15 mmol) gave, after purification by FC (PE/Et_2O 1:2), title compound **17b** as colourless oil as a (7.3:1) mixture with diethyl 2-((2*E*,4*E*)-*N*-benzylhexa-2,4-dienamido)malonate (349 mg, 0.93 mmol, 80%). An analytically pure sample was obtained by preparative HPLC (97:3, hexane:IPA). R_f = 0.47 (PE/Et_2O 1:2).

^{1}H-NMR (500 MHz, $CDCl_3$): 7.37-7.25 (*m*, 5H, H_{ar}), 5.55 (*s*, 1H, CH), 4.75 (*s*, 2H, CH_2Ph), 4.16-4.06 (*m*, 2H, OC*H*H), 4.05-3.97 (*m*, 2H, OCH*H*), 2.61-2.57 (*m*, 2H, CH_2CO), 2.52-2.47 (*m*, 2H, $CCCH_2$), 1.75 (*t*, 3H, *J* = 2.3 Hz, CH_3), 1.19 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 173.0 (CO), 166.2 (2xCO), 136.3 (C_{ar}), 128.6 (2xCH_{ar}), 127.5 (CH_{ar}), 126.3 (2xCH_{ar}), 77.7 (C_{sp}), 76.2 (C_{sp}), 62.0 (2xCH_2), 60.9 (CH), 50.5 (CH_2), 32.9 (CH_2), 14.7 (CH_2), 13.8 (2xCH_3), 3.5 (CH_3). IR (film): 3585w, 2983m, 2922m, 2360m (C≡C), 2341m, 1739s (C=O, ester), 1665s (C=O, amide). MS (ESI+): 360.2 (14, $[M+H]^+$), 382.2 (72, $[M+Na]^+$), 741.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{20}H_{25}NNaO_5$ ($[M+Na]^+$) 382.1625, found 382.1624.

3. Synthesis of aminomalonates

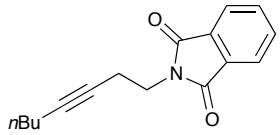
Oct-3-yn-1-yl methanesulfonate



Oct-3-yn-1-ol (10.0 g, 79.2 mmol) and triethylamine (12.0 g, 119 mmol) were dissolved in DCM (80 mL) at 0 ºC and allowed to stir for 1 h. Methanesulfonyl chloride (9.07g, 79.2 mmol) was added and the mixture allowed to stir for 2 h at room temperature. Water (60 mL) was added and the organic layer separated, washed successively with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under

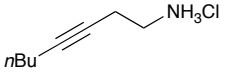
reduced pressure to yield the title compound (16.2 g, 79.2 mmol, 100%) as a yellow oil which was used without further purification. R_f = 0.30 (PE/Et_2O 1:1).
^{1}H-NMR (400 MHz, $CDCl_3$): 4.20 (*t*, 2H, *J* = 6.8 Hz, CH_2O), 2.99 (*s*, 3H, SO_2CH_3), 2.56 (*tt*, 2H, *J* = 6.8, 2.2 Hz, CH_2CH_2O), 2.10-2.07 (*m*, 2H, $CH_3CH_2CH_2CH_2$), 1.43-1.29 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 0.85 (*t*, 3H, *J* = 7.2 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 82.9 (C_{sp}), 74.1 (C_{sp}), 68.1 (CH_2), 37.4 (CH_3), 30.7 (CH_2), 21.8 (CH_2), 19.9 (CH_2), 18.2 (CH_2), 13.5 (CH_3). IR (film): 3472w, 3061w, 2957m, 2933m, 2872m, 1774m, 1717s, 1615w. MS (ESI+): 227.1 (87, $[M+Na]^+$). HRMS (ESI): calculated for $C_9H_{16}NaO_3S$ ($[M+Na]^+$) 227.0712, found 227.0712.

2-(Oct-3-yn-1-yl)isoindoline-1,3-dione



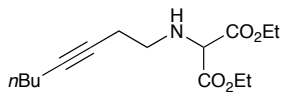
Potassium phthalimide (16.1 g, 87.0 mmol) and sodium iodide (1.30 g, 8.7 mmol) were suspended in DMF (200 mL) and then oct-3-yn-1-yl methanesulfonate (18.5 g, 91 mmol) was added dropwise. The reaction mixture was then heated to 100 ºC for 4 h. The reaction mixture was allowed to cool to room temperature and then water (500 mL) was added to dissolve the precipitate. The mixture was extracted with DCM (3 × 200 mL) and the combined organic layers were washed with saturated aqueous ammonium chloride solution (200 mL) and the solvent removed under reduced pressure. The resulting mixture was dissolved in EtOAc (50 mL) and water (50 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product. Further purification was achieved by FC (PE/Et_2O 4:1) to yield the title product as a waxy solid (11.0 g, 42.9 mmol, 47%). R_f = 0.38 (PE/Et_2O 3:1).
^{1}H-NMR (400 MHz, $CDCl_3$): 7.86-7.82 (*m*, 2H, H_{ar}), 7.73-7.70 (*m*, 2H, H_{ar}), 3.83 (*t*, 2H, *J* = 7.1 Hz, CH_2N), 2.56 (*t*, 2H, *J* = 7.1 Hz, CH_2CH_2N), 2.06 (*t*, 2H, *J* = 6.9 Hz, $CH_2CH_2CH_2CH_3$), 1.39-1.23 (*m*, 4H, $CH_2CH_2CH_2CH_3$), 0.81 (*t*, 3H, *J* = 7.1 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.1 (2xCO), 133.9 (2xCH_{ar}), 132.1 (2xC_{ar}), 123.1 (2xCH_{ar}), 82.4 (C_{sp}), 75.8 (C_{sp}), 37.1 (CH_2), 30.8 (CH_2), 21.8 (CH_2), 18.6 (CH_2), 18.3 (CH_2), 13.5 (CH_3). IR (film): 3472w, 2957m, 2933m, 2872m, 1774s (C=O), 1717s (C=O). MS (ESI+): 256.2 (25, $[M+H]^+$), 278.1 (74, $[M+Na]^+$), 533.3 (67, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{16}H_{17}NNaO_2$ ($[M+Na]^+$) 278.1151, found 278.1151.

Oct-3-yn-1-aminium chloride



2-(Oct-3-yn-1-yl)isoindoline-1,3-dione (11.0 g, 42.9 mmol) was dissolved in ethanol (360 mL) and hydrazine hydrate (3.1 mL, 64.4 mmol) was added. The reaction was stirred for 3 days at room temperature after which time a white precipitate had formed. Water (360 mL) was added to dissolve the precipitate and concentrated hydrochloric acid (13 mL) was added. The reaction was allowed to stir for a further 24 h after which time a white precipitate had formed. The precipitate was removed by filtration and ethanol was removed under reduced pressure. Sodium hydroxide (7 g) was added to the remaining mixture and the aqueous was extracted with diethyl ether (10×50 mL) until no amine remained in the aqueous layer. The combined organic extracts were treated with anhydrous HCl (prepared by dripping concentrated H_2SO_4 on NaCl) until acidic. The amine salt was precipitated and collected by filtration (3.81 g, 23.6 mmol, 55%). mp 157.5-158.9 ºC.
^{1}H-NMR (400 MHz, $CDCl_3$): 8.40 (*s*, 3H, NH_3), 3.14 (*s*, 2H, CH_2N), 2.67 (*s*, 2H, CH_2CH_2N), 2.19 (*t*, 2H, *J* = 7.0 Hz, $CH_3CH_2CH_2CH_2$), 1.52-1.34 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 0.91 (*t*, 3H, *J* = 7.2, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 84.4 (C_{sp}), 73.8 (C_{sp}), 39.3 (CH_2), 39.3 (CH_2), 30.7 (CH_2), 22.0 (CH_2), 18.6 (CH_2), 18.2 (CH_2), 13.7 (CH_2). MS (ESI+): 126.1 (42, $[M+H]^+$).
The analytical data is in accordance with literature values.[4]

Diethyl 2-(oct-3-yn-1-ylamino)malonate

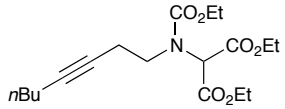


Oct-3-yn-1-aminium chloride (123) (3.72 g, 23.0 mmol) was dissolved in chloroform (100 mL). Diethyl 2-bromomalonate (3.60 g, 15.0 mmol) and triethylamine (5.31 g, 46.0 mmol) were added and the reaction was heated to 80 ºC. After 6 h the mixture was cooled to room temperature and water (100 mL) was added. The organic layer was separated and the aqueous portion was extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$) before removing the solvent under

reduced pressure. The crude product was purified by FC (PE/Et_2O 3:1) to give the title compound as a colourless oil (1.70 g, 6.33 mmol, 28%). R_f = 0.23 (PE/Et_2O, 3:1).
^{1}H-NMR (400 MHz, $CDCl_3$): 4.22-4.11 (*m*, 4H, 2xCH_2O), 4.00 (*s*, 1H, CH), 2.65-2.63 (*m*, 2H, CH_2N), 2.33-2.26 (*m*, 2H, CH_2CH_2N), 2.06-2.03 (*m*, 2H, $CH_3CH_2CH_2CH_2$), 1.40-1.25 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 1.23-1.14 (*m*, 6H, 2xCH_3), 0.82-0.79 (*m*, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.3 (2xCO), 81.8 (C_{sp}), 77.0 (C_{sp}), 64.8 (CH), 61.6 (2xCH_2), 46.7 (CH_2), 30.8 (CH_2), 21.8 (CH_2), 19.1 (CH_2), 18.2 (CH_2), 13.9 (2xCH_3), 13.4 (CH_3). IR (film): 3334m (N-H), 2980s, 2959s, 2934s, 2872m, 1739s, 2359w (C-C), 1738s (C=O). MS (ESI+): 284.2 (96, $[M+H]^+$) 306.1 (100, $[M+Na]^+$), 589.4 (75, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{15}H_{25}NNaO_4$ ($[M+Na]^+$) 306.1676, found 306.1674.

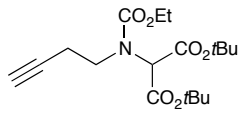
General Procedure for Carbamate Formation
Aminomalonate (1.0 eq.) was dissolved in DCM (2 mL/mmol) and saturated $NaHCO_3$ solution (2 mL/mmol). Chloroformate (1.5 eq.) was added dropwise and the reaction was allowed to stir for 3 h. The reaction mixture was then filtered through a silica pad, eluting with diethyl ether. The solvent was removed under reduced pressure to give the crude product

Diethyl 2-((ethoxycarbonyl)(oct-3-yn-1-yl)amino)malonate 15c



Prepared from diethyl 2-(oct-3-yn-1-ylamino)-malonate (269 mg, 0.75 mmol) and ethyl chloroformate (163 mg, 1.50 mmol) using GP5. The crude product was purified by FC (PE/Et_2O, 2:1) to give the title compound **15c** as a colourless oil (293 mg, 0.68 mmol, 91%). R_f = 0.34 (PE/Et_2O, 2:1).
Approximaetly 2:1 mixture of rotamers at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): 5.21 & 4.92 (*s*, 1H, CH), 4.27-4.05 (*m*, 6H, 3xCH_2O), 3.45-3.38 (*m*, 2H, CH_2N), 2.43-2.39 (*m*, 2H, CH_2CH_2N), 2.07-2.06 (*m*, 2H, $CH_3CH_2CH_2CH_2$), 1.43-1.30 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 1.25 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3), 1.15 (*t*, 3H, *J* = 7.0 Hz, CH_3), 0.84 (*t*, 3H, *J* = 7.0 Hz, C$H_3CH_2CH_2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.44/166.18 (2xCO) 156.3/155.2 (CO), 81.8 (C_{sp}), 76.9/76.6 (C_{sp}), 63.6/63.0 (CH) 62.3/62.0 (3xCH_2), 48.2/47.0 (CH_2), 31.0 (CH_2), 21.9 (CH_2), 19.3 (CH_2), 18.7/18.3 (CH_2), 14.5/14.3 (CH_3), 13.9 (2xCH_3), 13.5 (CH_3). IR (film): 2982s, 2960s, 2935s, 2874s, 2737m, 2257w (C-C), 1744s (C=O, ester), 1713s (C=O, carbamate). MS (ESI+): 356.2 (23, $[M+H]^+$), 378.1 (100, $[M+Na]^+$), 733.4 (78, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{18}H_{29}NNaO_6$ ($[M+Na]^+$) 378.1887, found 378.1888.

Di-tert-butyl 2-(but-3-yn-1-yl(ethoxycarbonyl)amino)malonate 15b



Di-*tert* -butyl 2-(but-3-yn-1-ylamino)malonate (566 mg, 2.00 mmol) and ethyl chloroformate using gave, after purification by FC (PE/Et_2O 4:1), the title compound as a colourless oil (525 mg, 1.48 mmol, 74%). R_f = 0.53 (PE/Et_2O 4:1).
Approximatelly 2:1 mixture of rotamers at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): 5.18 & 4.87 (*s*, 1H, $(OC)_2CH$), 4.21-4.10 (*m*, 2H, OCH_2), 3.49 (*t*, 2H, *J* = 8.0 Hz, CH_2N), 2.53-2.51 (*m*, 2H, $CCCH_2$), 1.97 & 1.95 (*s*, 1H, CH), 1.48 (*s*, 18H, 2x$(CH_3)_3$), 1.28 & 1.21 (*t*, 3H, *J* = 7.1 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.7 & 165.3 (2xCO), 156.3 & 155.0 (CO), 82.9 (2xC), 81.3 (C_{sp}), 69.9 (C_{sp}), 64.8 & 64.1 (CH), 62.2 & 62.0 (CH_2), 46.9 & 45.8 (CH_2), 27.8 (6xCH_3), 19.1 & 8.5 (CH_2), 14.5 & 14.4 (CH_3). IR (film): 3287m (C≡C-H), 2981s, 2936m, 2360w (C≡C), 1736s (C=O, ester), 1710s (C=O, carbamate). MS (ESI+): 378.2 (86, $[M+Na]^+$), 733.3 (53, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{18}H_{29}NNaO_6$ ($[M+Na]^+$) 378.1887, found 378.1888.

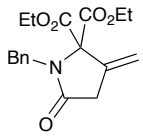
4. Cyclisation reactions

Procedure A
Amidomalonate (1.0 eq.) and manganese(III) acetate (2.0 eq.) were dissolved in degassed alcohol solvent (20 mL/mmol malonate). The solution was heated to 80 ºC and allowed to stir for 15 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The resulting residue was suspended in diethyl ether and filtered through a silica pad, eluting with diethyl ether. The solvent was removed under reduced pressure to yield the crude product.

Procedure B

Amidomalonate (1.0 eq.) and manganese(III) acetate (2.0 eq.) were dissolved in degassed alcohol solvent (20 mL/mmol malonate). The reaction mixture was allowed to stir at room temperature for 2 h and then filtered through a silica pad eluting with diethyl ether. The solvent was removed under reduced pressure to yield the crude product.

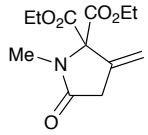
Diethyl 1-benzyl-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate 8a



Synthesised from diethyl 2-(*N*-benzylbut-3-ynamido)malonate **7a** (132 mg, 0.40 mmol, 1.0 eq.) using *Procedure A* with ethanol as solvent. Purification by FC (PE/Et_2O 1:2) gave the title compound **8a** as a colourless oil (97.6 mg, 0.29 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.28-7.25 (*m*, 2H, H_{ar}), 7.21-7.16 (*m*, 3H, H_{ar}), 5.57 (*t*, 1H, *J* = 2.5 Hz, CH_{olef}), 5.42 (*t*, 1H, *J* = 2.1 Hz, CH_{olef}), 4.74 (*s*, 2H, CH_2Ar), 3.98-3.85 (*m*, 4H, 2xOCH_2), 3.32 (*t*, 2H, *J* = 2.5 Hz, CH_2CO), 1.11 (*t*, 6H, *J* = 7.1 Hz, 2xCH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.6 (CO), 166.7 (CO), 136.7 (C_{olef}), 135.6 (CH_{ar}), 128.2 (2xCH_{ar}), 127.2 (2xCH_{ar}), 127.1 (CH_{ar}), 114.7 (CH_{olef}), 75.8 (C), 62.4 (CH_2), 45.8 ($ArCH_2$), 35.6 (CH_2), 13.6 (CH_3). IR (film): 2982m, 1740s, 1716s, 1666w, 1386m, 1263m, 1241m, 1178m, 1050m, 711w. MS (ESI+): 332.16 (22, $[M+H]^+$), 354.13 (58, $[M+Na]^+$), 390.19 (74), 433.24 (77), 663.29 (57), 685.18 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{18}H_{21}NNaO_5$ ($[M+Na]^+$) 354.1312, found 354.1311.

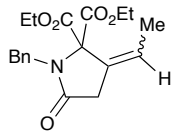
Diethyl 1-methyl-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate 8b



Synthesised from diethyl 2-(*N*-methylbut-3-ynamido)malonate **7b** (255 mg, 1.0 mmol, 1.0 eq.) using *Procedure A* with ethanol as solvent. Purification by FC (PE/Et_2O 3:2) gave the title compound **8b** as a colourless oil (170.7 mg, 0.67 mmol, 67%).

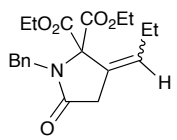
^{1}H-NMR (400 MHz, $CDCl_3$): 5.58 (*td*, 1H, *J* = 2.7, 0.5 Hz, H_{olef}), 5.38 (*td*, 1H, *J* = 2.4, 0.5 Hz, H_{olef}), 4.35-4.24 (*m*, 4H, 2xOCH_2), 3.20 (*t*, 2H, *J* = 2.1 Hz, CH_2CO), 2.98 (*s*, 3H, NCH_3), 1.31 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.0 (CO), 166.5 (2xCO), 135.5 (C_{olef}), 114.2 (CH_{olef}), 62.6 (2xCH_2), 35.6 (CH_2), 28.3 (CH_3), 13.9 (2xCH_3). IR (film): 2984s, 2940m, 1739s, 1715s, 1667m, 1467w, 1447w, 1422w, 1372s, 1293m, 1238s, 1118m, 1055s, 950w, 913w, 858w, 678w. MS (ESI+): 256 (18, $[M+H]^+$), 278.09 (63, $[M+Na]^+$), 511.20 (94, $[2M+H]^+$), 533.12 (100, $[2M+Na]^+$), 788.30 (55, $[3M+Na]^+$). HRMS (ESI): calculated for $C_{12}H_{17}NNaO_5$ ($[M+Na]^+$) 278.0999, found 278.1002.

Diethyl 3-ethylidene-1-methyl-5-oxopyrrolidine-2,2-dicarboxylate 10a



Synthesised from diethyl 2-(*N*-benzylpent-3-ynamido)malonate **9a** (173 mg 0.5 mmol, 1.0 eq.) using *Procedure A* with ethanol as solvent. Purification by FC (PE/Et_2O 1:2) gave the title compound **10a** (134.4 mg, 0.39 mmol, 78%) as a clear oil, isolated as an inseparable mixture of isomers *E*/*Z* = 1.0 : 3.8: ^{1}H-NMR (400 MHz, $CDCl_3$): *E*-isomer: 7.27-7.14 (*m*, 5H, H_{ar}), 5.96 (*qt*, 1H, *J* = 6.8, 2.7 Hz, H_{olef}), 4.71 (*s*, 2H, CH_2Ph), 3.99-3.76 (*m*, 4H, CH_2O), 3.22-3.19 (*m*, 2H, CH_2CO), 1.72 (*dt*, 1H, *J* = 6.9, 1.8 Hz, CH_3), 1.09 (*t*, 6H, *J* = 6.9 Hz, 2xCH_3). *Z*-isomer: 7.27-7.14 (*m*, 5H, H_{ar}), 5.74 (*qt*, 1H, *J* = 7.4, 2.5 Hz, H_{olef}), 4.64 (*s*, 2H, CH_2Ph), 3.99-3.76 (*m*, 4H, CH_2O), 3.25-3.22 (*m*, 2H, CH_2CO), 1.67 (d*t*, 1H, *J* = 7.4, 2.3 Hz, CH_3), 1.11 (*t*, 6H, *J* = 6.9 Hz, 2xCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): *E*-isomer: 173.9 (2xCO), 167.1 (CO), 136.8 (CH_{olef}), 128.2 (2xCH_{ar}), 127.2 (CH_{ar}), 127.0 (2xCH_{ar}), 127.0 (C_{ar}), 125.1 (C_{olef}), 75.6 (C), 62.3 (2xCH_2), 45.8 (CH_2), 32.9 (CH_2), 15.2 (CH_3), 13.6 (2xCH_3). *Z*-isomer: 173.9 (2xCO), 166.7 (CO), 136.5 (CH_{olef}), 128.1 (2xCH_{ar}), 127.8 (2xCH_{ar}), 127.2 (CH_{ar}), 126.4 (C_{ar}), 125.9 (C_{olef}), 74.8 (C), 62.3 (2xCH_2), 45.5 (CH_2), 36.2 (CH_2), 15.1 (CH_3), 13.7 (2xCH_3).
IR (film): 3063w, 3031w, 2982m, 2938w, 1737s, 1712s, 1496w, 1433w, 1389m, 1367w, 1351w, 1296w, 1244s, 1175m, 1051s, 700m. MS (ESI+): 317.25 (70), 346.18 (28, $[M+H]^+$), 368.16 (100, $[M+Na]^+$), 447.30 (41), 713.33 (12, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{19}H_{23}NNaO_5$ ($[M+Na]^+$) 368.1468, found 368.1464.

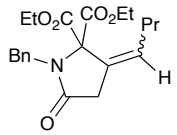
Diethyl 1-benzyl-5-oxo-3-propylidenepyrrolidine-2,2-dicarboxylate 10b



Prepared from diethyl 2-(*N*-benzylhex-3-ynamido)malonate **9b** (180 mg, 0.50 mmol) using *Procedure B* with ethanol as the solvent. Purified by FC (PE/Et_2O 1:1) to give the title **10b** compound as a colourless oil (155 mg,

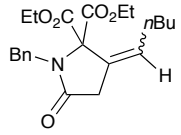
0.43 mmol, 86%) with a 1:4.7 *E*:*Z* ratio, characterisation data is for the mixture. R_f = 0.28 (PE/Et_2O 1:1).
^{1}H-NMR (400 MHz, $CDCl_3$): *E*-isomer: 7.23-7.11 (*m*, 5H, H_{ar}), 5.84 (*t*, 1H, *J* = 7.4 Hz, H_{olef}), 4.68 (*s*, 2H, CH_2Ph), 3.94-3.71 (*m*, 4H, 2xCH_2O), 3.16 (*s*, 2H, CH_2CO), 2.09-2.00 (*m*, 2H, C=CHC$H_2$$CH_3$), 1.07 (*t*, 6H, *J* = 7.2 Hz, 2xCH_2CH_3), 0.97 (*t*, 6H, *J* = 7.5 Hz, OCH_2CH_3), 0.82 (*t*, 3H, *J* = 7.0 Hz, CH_3). *Z*-isomer: 7.23-7.11 (*m*, 5H, H_{ar}), 5.56 (*t*, 1H, *J* = 7.8 Hz, H_{olef}), 4.60 (*s*, 2H, CH_2Ph), 3.94-3.71 (*m*, 4H, 2xCH_2O), 3.20 (*s*, 2H, CH_2CO), 2.09-2.00 (*m*, 2H, C=CHC$H_2$$CH_3$), 1.07 (*t*, 6H, *J* = 7.2 Hz, 2xCH_2CH_3), 0.90 (*t*, 3H, *J* = 7.4 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): *E*-isomer: 173.8 (CO), 167.1 (CO), 136.6 (C_{ar}), 132.0 (CH_{olef}), 128.1 (2xCH_{ar}), 127.1 (2xCH_{ar}), 127.0 (CH_{ar}), 125.8 (C_{olef}), 75.5 (C), 62.2 (2xCH_2), 45.8 (CH_2), 32.8 (CH_2), 23.1 (CH_2), 13.6 (2xCH_3), 13.0 (CH_3). *Z*-isomer: 173.8 (CO), 166.9 (CO), 136.8 (C_{ar}), 132.9 (CH_{olef}), 128.1 (2xCH_{ar}), 127.8 (2xCH_{ar}), 127.1 (CH_{ar}), 124.7 (C_{olef}), 74.8 (C), 62.3 (2xCH_2), 45.5 (CH_2), 36.2 (CH_2), 23.0 (CH_2), 13.6 (2xCH_3), 13.0 (CH_3). IR (film): 3089m, 3064m, 3032m, 2979s, 2937m, 2875m, 1739s (C=O). MS (ESI+): 360.2 (80, $[M+H]^+$), 382.2 (78, $[M+Na]^+$), 719.4 (97, $[2M+H]^+$), 741.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{20}H_{25}NNaO_5$ ($[M+Na]^+$) 382.1625, found 382.1624.

Diethyl 1-benzyl-5-oxo-3-butylidenepyrrolidine-2,2-dicarboxylate 10c



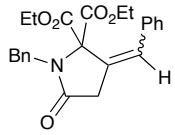
Prepared from diethyl 2-(*N*-benzylhept-3-ynamido)malonate **9c** (187 mg, 0.50 mmol) using *Procedure B* with ethanol as the solvent. Purified by FC (PE/Et_2O 1:1) to give the title compound **10c** as a colourless oil (136 mg, 0.36 mmol, 72%) with a 1:2.9 *E*:*Z* ratio, characterisation data is for the mixture. R_f = 0.38 & 0.31 (PE/Et_2O 1:1).
^{1}H-NMR (400 MHz, $CDCl_3$): *E*-isomer: 7.27-7.12 (*m*, 5H, H_{ar}), 5.85 (*t*, 1H, *J* = 7.4 Hz, H_{olef}), 4.68 (*s*, 2H, CH_2Ph), 3.95-3.71 (*m*, 4H, 2xCH_2O), 3.17 (*s*, 2H, CH_2CO), 2.05-1.96 (*m*, 2H, C$H_2$$CH_2CH_3$), 1.42 (*tq*, 2H, *J* = 7.3, 7.3 Hz, CH_2C$H_2$$CH_3$), 1.09-1.04 (*m*, 6H, 2xCH_3), 0.89-0.82 (*m*, 3H, CH_2CH_2CH_3). *Z*-isomer: 7.27-7.12 (*m*, 5H, H_{ar}), 5.56 (*t*, 1H, *J* = 7.8 Hz, H_{olef}), 4.60 (*s*, 2H, CH_2Ph), 3.95-3.71 (*m*, 4H, 2xCH_2O), 3.21 (*s*, 2H, CH_2CO), 2.05-1.96 (*m*, 2H, C$H_2$$CH_2CH_3$), 1.32 (*tq*, 2H, *J* = 7.3, 7.3 Hz, CH_2C$H_2$$CH_3$), 1.09-1.04 (*m*, 6H, 2xCH_3), 0.89-0.82 (*m*, 3H, CH_2CH_2CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): *E*-isomer: 173.9 (2xCO), 167.2 (CO), 136.8 (C_{ar}), 130.5 (CH_{olef}), 128.2 (2xCH_{ar}), 127.2 (2xCH_{ar}), 127.0 (CH_{ar}), 126.6 (C_{olef}), 75.6 (C), 62.2 (2xCH_2), 33.0 (CH_2), 31.6 (CH_2), 21.8 (CH_2), 13.8 (2xCH_3), 13.5 (CH_3). *Z*-isomer: 173.9 (2xCO), 166.8 (CO), 136.6 (C_{ar}), 131.4 (CH_{olef}), 128.1 (2xCH_{ar}), 127.8 (2xCH_{ar}), 127.1 (CH_{ar}), 125.2 (C_{olef}), 74.9 (C), 62.3 (2xCH_2), 45.5 (CH_2), 36.2 (CH_2), 31.5 (CH_2), 21.9 (CH_2), 13.6 (3xCH_3). IR (film): 3089m, 3064m, 3032m, 2962s, 2933s, 2873m, 1739s (C=O). MS (ESI+): 374.2 (45, $[M+H]^+$), 396.2 (53, $[M+Na]^+$), 747.4 (78, $[2M+H]^+$), 769.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{21}H_{27}NNaO_5$ ($[M+Na]^+$) 396.1781, found 396.1784.

Diethyl 1-benzyl-5-oxo-3-pentylidenepyrrolidine-2,2-dicarboxylate 10d



Synthesised from diethyl 2-(*N*-benzyloct-3-ynamido)malonate (194 mg, 0.50 mmol) using *Procedure A* with ethanol as solvent. Purification by FC (PE/Et_2O 2:3) gave the title compound **10d** as a colourless oil (140 mg, 0.36 mmol, 73%) with a 1:3.0 *E*:*Z* ratio. R_f = 0.26 & 0.40 (PE/Et_2O 1:1).
^{1}H-NMR (400 MHz, $CDCl_3$): *Z*-isomer: 7.30-7.16 (*m*, 5H, CH_{ar}), 5.64 (*t*, 1H, *J* = 7.6 Hz, H_{olef}, 4.64 (*s*, 2H, CH_2Ph), 3.99-3.91 (*m*, 2H, CH_2O), 3.83-3.75 (*m*, 2H, CH_2O), 3.26 (*s*, 2H, CH_2CO), 2.07-2.02 (*m*, 2H, $CH_3CH_2CH_2CH_2$), 1.32-1.25 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 1.12 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3), 0.88 (*t*, 3H, *J* = 6.8 Hz, $CH_3CH_2CH_2CH_2$). *E*-isomer: 7.30-7.16 (*m*, 5H, H_{ar}), 5.91-5.86 (*m*, 1H, H_{olef}), 4.72 (*s*, 2H, CH_2Ph), 3.96-3.84 (*m*, 4H, 2xCH_2O), 3.21 (*s*, 2H, CH_2CO), 2.09 (*q*, 2H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$), 1.48-1.44 (*m*, 4H, $CH_3CH_2CH_2CH_2$), 1.10 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3), 0.90 (*t*, 3H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): *Z*-isomer: 173.9 (CO), 166.8 (2xCO), 136.7 (C_{ar}), 131.6 (C_{olef}), 128.1 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.2 (CH_{ar}), 125.1 (C_{olef}), 74.9 (C), 62.3 (2xCH_2), 45.5 (CH_2), 36.3 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 22.4 (CH_2), 13.9 (CH_3), 13.7 (CH_3). *E*-isomer: 173.9 (CO), 167.2 (2xCO), 136.8 (C_{ar}), 130.7 (C_{olef}), 128.2 (2xCH_{ar}), 127.2 (2xCH_{ar}), 127.0 (CH_{ar}), 126.3 (C_{olef}), 75.6 (C), 62.2 (2xCH_2), 45.9 (CH_2), 33.0 (CH_2), 30.7 (CH_2), 29.7 (CH_2), 22.1 (CH_2), 13.9 (2xCH_3), 13.6 (CH_3). IR(film): 3400b, 2959m, 2932m, 2872w, 1740s (C=O, ester), 1713s (C=O, amide). MS (ESI+): 410.2 (100, $[M+Na]^+$). HRMS (ESI): calculated for $C_{22}H_{29}NNaO_5$ ($[M+Na]^+$) 410.1938, found 410.1939.

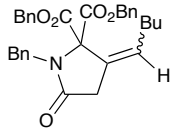
Diethyl 1-benzyl-3-benzylidene-5-oxopyrrolidine-2,2-dicarboxylate 10e



Synthesised from diethyl 2-(*N*-benzyl-4-phenylbut-3-ynamido)malonate **9e** (203 mg, 0.49 mmol) using *Procedure B* with ethanol as the solvent. Purified by FC (PE/Et_2O 1:1) to give the title compound **10e** as a colourless oil (131 mg, 0.32 mmol, 65%) with a 1:3.0 *E*:*Z* ratio, characterisation data is for the mixture. R_f = 0.26 & 0.32 (PE/Et_2O 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): *E*-isomer: 7.47-7.16 (*m*, 10H, H_{ar}), 6.70 (*s*, 1H, H_{olef}), 4.26 (*s*, 2H, CH_2Ph), 4.00-3.89 (*m*, 4H, 2xCH_2O), 3.56 (*s*, 2H, CH_2Ph), 0.87 (*t*, 6H, *J* = 7.2 Hz, 2xCH_3). *Z*-isomer: 7.47-7.16 (*m*, 10H, H_{ar}), 6.84 (*s*, 1H, H_{olef}), 4.77 (*s*, 2H, CH_2Ph), 3.74-3.65 (*m*, 2H, CH_2O), 3.61-3.53 (*m*, 2H, CH_2O), 3.40-3.39 (*m*, 2H, CH_2Ph), 1.12 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). The unambiguous assignment of the aromatic carbons was not possible. ^{13}C-NMR (100 MHz, $CDCl_3$): 173.6 (*E*-CO), 173.6 (*Z*-CO), 167.0 (*E*-2xCO), 166.1 (*Z*-2xCO), 136.6 (*E*-Ar), 136.4 (*Z*-Ar), 135.6 (*E*-Ar), 135.0 (*Z*-Ar), 129.7 (*Z*-C_{olef}), 129.2 (*E*-C_{olef}), 128.7 (Ar), 128.7 (Ar), 128.6 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 128.1 (Ar), 127.9 (Ar), 127.6 (Ar), 127.3 (Ar), 127.2 (*Z*-CH_{olef}), 127.1 (*E*-CH_{olef}), 77.4 (*E*-C), 75.2 (*Z*-C), 62.5 (*E*-2xCH_2), 62.4 (*Z*-2xCH_2), 45.9 (*E*-CH_2), 45.7 (*Z*-CH_2), 38.7 (*Z*-CH_2), 35.1 (*E*-CH_2), 13.7 (*E*-2xCH_3), 13.4 (*Z*-2xCH_3). IR (film): 3467br, 3063m, 3030m, 2983s, 2938m, 2904m, 1716s (C=O). MS (ESI+): 430.2 (26, $[M+Na]^+$), 446.1 (52, $[M+K]^+$), 837.3 (98, $[2M+Na]^+$, 98%), 853.3 (100, $[2M+K]^+$). HRMS (ESI): calculated for $C_{24}H_{25}NNaO_5$ ($[M+Na]^+$) 430.1625, found 430.1618.

Dibenzyl 1-benzyl-5-oxo-3-pentylidenepyrrolidine-2,2-dicarboxylate 12

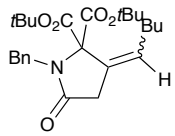


Synthesised from dibenzyl 2-(*N*-benzyloct-3-ynamido)malonate **11** (282 mg, 0.56 mmol) using *Procedure B* with ethanol as the solvent. Purified by FC (PE/Et_2O 1:1) to give the title compound as a colourless oil (218 mg, 0.44 mmol, 79%) with a 1:3.5 *E*:*Z* ratio. R_f = 0.21 & 0.29 (PE/Et_2O 1:1).

The analytical data is given for the *E*/*Z*-mixture:

^{1}H-NMR (400 MHz, $CDCl_3$): *E*-isomer: 7.32-7.12 (*m*, 15H, H_{ar}), 5.80 (*t*, 1H, *J* = 7.5 Hz, H_{olef}), 4.90-4.84 (*m*, 4H, 2xOCH_2Ph), 4.71 (*s*, 2H, NCH_2Ph), 3.18 (*s*, 2H, CH_2CO), 1.99 (*q*, 2H, *J* = 7.5 Hz, CH_2CH_2CH_2CH_3), 1.33-1.16 (*m* 4H, CH_2CH_2CH_2CH_3), 0.83 (*t*, 3H, *J* = 7.0 Hz, CH_3). *Z*-isomer: 7.32-7.12 (*m*, 15H, H_{ar}), 5.55 (*t*, 1H, *J* = 7.6 Hz, H_{olef}), 4.76-4.64 (*m*, 4H, 2xOCH_2Ph), 4.64 (*s*, 2H, NCH_2Ph), 3.23 (*s*, 2H, CH_2CO), 1.77 (*q*, 2H, *J* = 7.6 Hz, CH_2CH_2CH_2CH_3), 1.06-0.94 (*m*, 4H, CH_2CH_2CH_2CH_3), 0.69 (*t*, 3H, *J* = 7.0 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.0 (*Z*-CO), 173.9 (*E*-CO), 166.9 (*E*-2xCO), 166.6 (*Z*-2xCO), 136.6 (Ar), 136.4 (Ar), 134.6 (Ar), 134.5 (Ar), 132.1 (Ar), 131.1 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 126.9 (Ar), 126.0 (Ar), 124.6 (Ar), 76.9 (*E*-C), 74.8 (*Z*-C), 68.0 (*Z*-2xCH_2), 67.8 (*Z*-2xCH_2), 45.8 (*E*-CH_2), 45.6 (*Z*-CH_2), 36.2 (*Z*-CH_2), 33.0 (*E*-CH_2), 30.6 (*E*-CH_2),30.6 (*Z*-CH_2), 29.4 (*E*-CH_2), 29.4 (*Z*-CH_2), 22.3 (*Z*-CH_2), 22.2 (*E*-CH_2), 13.9 (*E*-CH_3), 13.8 (*Z*-CH_3). IR (film): 3065m, 3033m, 2957s, 2929s, 2871m, 1713s (C=O). MS (ESI+): 534.2 (100, $[M+Na]^+$). HRMS (ESI): calculated for $C_{32}H_{33}NNaO_5$ ($[M+Na]^+$) 534.2251, found 534.2263.

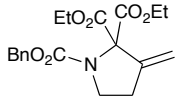
Di-*tert*-butyl 1-benzyl-5-oxo-3-pentylidenepyrrolidine-2,2-dicarboxylate 14



Synthesised from di-*tert*-butyl 2-(*N*-benzyloct-3-ynamido)malonate **13** (215 mg, 0.49 mmol) using *Procedure B* with ethanol as solvent. Purified by FC (PE/Et_2O 1:1) to give the title compound **14** as a colourless oil (179 mg, 0.40 mmol, 82%) with a 1:6.6 *E*:*Z* ratio. NMR data is for the (*Z*)-product. R_f = 0.38 & 0.44 (PE/Et_2O 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27-7.16 (*m*, 5H, H_{ar}), 5.69 (*t*, 1H, *J* = 7.6 Hz, H_{olef}), 4.64 (*s*, 2H, CH_2Ph), 3.26 (*s*, 2H, CH_2CO), 2.16-2.07 (*m*, 2H, CH_2CH_2CH_2CH_3), 1.42-1.18 (*m*, 4H, CH_2CH_2CH_2CH_3), 1.30 (*s*, 18H, 2xC(CH_3)$_3$), 0.90 (*t*, 3H, *J* = 7.1 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.4 (CO), 165.6 (2xCO), 136.9 (C_{ar}), 131.5 (CH_{olef}), 128.3 (2xCH_{ar}), 126.8 (CH_{ar}), 126.5 (2xCH_{ar}), 125.1 (C_{olef}), 83.5 (2xC), 76.8 (C), 46.0 (CH_2), 36.4 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 27.4 (6xCH_3), 22.6 (CH_3), 13.9 (CH_3). IR (film): 2978m, 2932m, 2873m, 1730s (C=O). MS (ESI+): 909.52 (100, $[2M+Na]^+$). HRMS (FI): calculated for $C_{26}H_{37}NO_5$ ($[M]^+$) 443.2673, found 443.2672.

1-Benzyl 2,2-diethyl 3-methylenepyrrolidine-1,2,2-tricarboxylate 16a

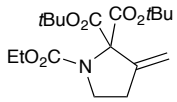


Diethyl 2-(((benzyloxy)carbonyl)(but-3-yn-1-yl)amino)malonate **15a** (181 mg, 0.50 mmol, 1.0 eq.) was dissolved in degassed EtOH (10 mL) and manganese(III) acetate (268 mg, 1.0 mmol, 2.0 eq.) was added. The

reaction mixture was heated to 80 ºC for 15 h and then allowed to cool. The reaction was filtered through a plug of silica (eluent: Et_2O) before removing the solvent. After purification by FC (PE/Et_2O 1:1) the title compound was obtained as a colorless oil (141.6 mg, 0.39 mmol, 78%).

Approximately 1:1 mixture of rotamers at 400 MHz at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): 7.40-7.27 (*m*, 5H, H_{ar}), 5.50 (*t*, 0.45H, *J* = 2.0 Hz, H_{olef}), 5.46 (*t*, 0.55H, *J* = 1.9 Hz, H_{olef}), 5.21-5.18 (*m*, 1.9H, CH_2Ar, CH_{olef}), 5.11 (*s*, 1.1H, CH_2Ar), 4.27-4.19 (*m*, 1.8H, 2xCH_2O), 4.12-3.98 (*m*, 2.2H, 2xCH_2O), 3.74 (*t*, 1.1H, *J* = 7.4 Hz, CH_2N), 3.72 (*t*, 0.9H, *J* = 7.5 Hz, CH_2N), 2.75-2.68 (*m*, 2H, CH_2C=C), 1.23 (*t*, 1.8H, *J* = 7.1 Hz, 2xCH_3), 1.11 (*t*, 2.2H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.8 (2xCO), 154.5/154.1 (CO), 146.0/145.0 (C_{olef}), 136.6/136.1 (C_{ar}), 128.4/128.3 (2xCH_{ar}), 128.1/128.0 (2xCH_{ar}), 128.0/127.9 (CH_{ar}), 111.6/111.5 (CH_{olef}), 73.7/72.9 (C), 67.3/67.2 (CH_2), 62.1/62.0 (2xCH_2), 46.3/45.8 (CH_2), 31.4/30.5 (CH_2), 13.9/13.8 (2xCH_3). IR (film): 2982m, 2902w, 1773s, 1714s, 1445w, 1409s, 1355s, 1233s, 1132w, 1064m, 1047m, 911w, 769w, 699m. MS (ESI+): 384.14 (16, $[M+Na]^+$), 420.21 (36), 463.22 (99), 745.19 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{19}H_{23}NNaO_6$ ($[M+Na]^+$) 384.1418, found 384.1417.

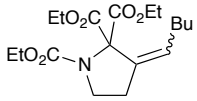
2,2-Di-*tert*-butyl 1-ethyl 3-methylenepyrrolidine-1,2,2-tricarboxylate 16b



Prepared from di-*tert* -butyl 2-(but-3-yn-1-ylamino)malonate (178 mg, 0.50 mmol) using *Procedure B* with ethanol as the solvent. Purified by FC (PE/Et_2O 3:1) to give the title compound as a colourless oil (138 mg, 0.39 mmol, 78%). R_f = 0.24 (PE/Et_2O 3:1).

Approximately 2:1 mixture of rotamers at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): 5.38 (*s*, 1H, C*H*H_{olef}), 5.09 (*s*, 1H, CH*H*$_{olef}$), 4.11 & 4.06 (*q*, 2H, *J* = 7.1 Hz, OCH_2), 3.61-3.54 (*m*, 2H, CH_2N), 2.61 (*t*, 2H, *J* = 6.1 Hz, CH_2), 1.41 & 1.40 (*s*, 18H, 2x$C(CH_3)_3$), 1.22 & 1.16 (*t*, 3H, *J* = 7.1 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.8 & 165.6 (2xCO), 154.6 (CO), 146.9 & 146.0 (C_{olef}) 110.6 & 110.4 (CH_{2olef}) 81.9 & 81.8 (2xC), 73.6 (C), 61.4 & 61.3 (CH_2), 46.0 & 45.7 (CH_2), 31.5 & 30.6 (CH_2) 27.6 (6xCH_3), 14.7 & 14.4 (CH_3). IR (film): 2979m, 2934m, 1715s (C=O). MS (ESI+): 356.2 (22, $[M+H]^+$), 378.2 (100, $[M+Na]^+$), 733.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{18}H_{29}NNaO_6$ ($[M+Na]^+$) 378.1887, found 378.1888.

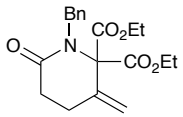
Triethyl 3-pentylidenepyrrolidine-1,2,2-tricarboxylate 16c



Prepared from diethyl 2-((ethoxycarbonyl)-(oct-3-yn-1-yl)amino)malonate **15c** (150 mg, 0.35 mmol) using *Procedure B* with ethanol as the solvent. Purified by FC (PE/Et_2O 1:1) to give the title compound **16c** as a colourless oil (103 mg, 0.24 mmol, 69%) with a 1:2.8 *E*:*Z* ratio, characterisation data is for the mixture. R_f = 0.30 (PE/Et_2O 1:1).

Mixture of diastereoisomers and rotamers (2:1) at room temperature: ^{1}H-NMR (400 MHz, $CDCl_3$): *E*-isomer: 5.81 (*t*, 1H, *J* = 7.6 Hz, H_{olef}), 4.24-4.05 (*m*, 6H, 3xCH_2O), 3.68/3.45 (*t*, 2H, *J* = 7.4 Hz, CH_2N), 2.65-2.53 (*m*, 2H, NCH_2CH_2), 2.03-1.97 (*m*, 2H, $CH_3CH_2CH_2CH_2$), 1.34-1.11 (*m*, 13H, 3xCH_3 and $CH_3CH_2CH_2CH_2$), 0.88-0.82 (*m*, 3H, $CH_3CH_2CH_2CH_2$). *Z*-isomer: 5.47 (*t*, 1H, *J* = 7.6 Hz, H_{olef}), 4.24-4.05 (*m*, 6H, 3xCH_2O), 3.61/3.56 (*t*, 2H, *J* = 7.4 Hz, CH_2N), 2.65-2.53 (*m*, 2H, NCH_2CH_2), 2.16-2.15 (*m*, 2H, $CH_3CH_2CH_2CH_2$), 1.34-1.11 (*m*, 13H, 3xCH_3 and $CH_3CH_2CH_2CH_2$), 0.88-0.82 (*m*, 3H, $CH_3CH_2CH_2CH_2$). Signals for the *E*/*Z*-isomer are not separately assigned: ^{13}C-NMR (100 MHz, $CDCl_3$): 167.7/167.5/167.3 (2xCO), 154.8/154.4 (CO), 137.0/135.8/134.7 (C_{olef}), 129.4/129.3/127.4 (CH_{olef}), 72.8/71.9 (C), 61.9/61.8/61.7/2x61.5/61.4 (3xCH_2), 46.1/45.7/45.3 (CH_2), 32.3/31.5/31.2/30.9/28.9/28.2/27.8/26.5 (3xCH_2), 28.9/28.2/27.8 (CH_2), 22.5/22.4/22.1 (CH_2), 14.6/2x14.4/14.3/13.8 (2xCH_3), 13.9 (2xCH_3). IR (film): 2981s, 2959s, 2933s, 2874m, 1775m, 1750s (C=O, ester), 1714s (C=O, carbamate). MS (ESI+): 356.2 (24, $[M+H]^+$), 378.1 (100, $[M+Na]^+$), 733.4 (78, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{18}H_{29}NNaO_6$ ($[M+Na]^+$) 378.1887, found 378.1888.

Diethyl 1-benzyl-3-methylene-6-oxopiperidine-2,2-dicarboxylate 18a

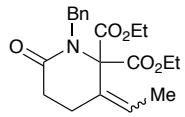


Synthesised from diethyl 2-(*N*-benzylpent-4-ynamido)malonate **17a** (194 mg, 0.56 mmol) using *Procedure A* with ethanol as the solvent. Purified by FC (PE/Et_2O 1:1) to give the title compound **18a** as a colourless oil (128 mg, 0.37 mmol, 66%). R_f = 0.20 (PE/Et_2O 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27-7.23 (*m*, 2H, H_{ar}), 7.23-7.13 (*m*, 3H, H_{ar}),

5.25 (*s*, 1H, H_{olef}), 5.24 (*s*, 1H, H_{olef}), 4.62 (*s*, 2H, CH_2Ph), 4.08-4.00 (*m*, 2H, OC*H*H), 3.90-3.81 (*m*, 2H, OCH*H*), 2.69-2.59 (*m*, 4H, CH_2CH_2), 1.11 (*t*, 6H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.8 (CO), 167.0 (2xCO), 139.4 (C_{olef}), 137.3 (C_{ar}), 128.0 (2xCH_{ar}), 127.1 (2xCH_{ar}), 126.7 (CH_{ar}), 114.8 (CH_{2olef}), 75.5 (C), 62.4 (2xCH_2), 50.0 (CH_2), 32.6 (CH_2), 29.4 (CH_2), 13.6 (2xCH_3). IR (film): 2982m, 2937w, 1735s (C=O, ester), 1669s (C=O, amide). MS (ESI+): 346.2 (38, $[M+H]^+$), 713.2 (100, $[2M+Na]^+$%). HRMS (ESI): calculated for $C_{19}H_{23}NNaO_5$ ($[M+Na]^+$) 368.1468, found 368.1470.

Diethyl 1-benzyl-3-ethylidene-6-oxopiperidine-2,2-dicarboxylate 18b



Synthesised from diethyl 2-(*N*-benzylhex-4-ynamido)malonate **17b** (20 mg, 0.054 mmol) using *Procedure A* with ethanol as the solvent and heating time reduced to 5 h. Purified by FC (PE/Et_2O 1:2) to yield product **18b** as a colourless oil (14.4 mg, 0.038 mmol, 71%) with a 1:5 *E*:*Z* ratio.

Characterisation data is for the mixture: ^{1}H-NMR (500 MHz, $CDCl_3$): *E*-isomer: 7.31-7.21 (*m*, 5H, H_{ar}), 5.76 (*t*, 1H, *J* = 6.9 Hz, H_{olef}), 4.63 (*s*, 2H, CH_2Ph), 4.13-4.04 (*m*, 2H, OC*H*H), 3.94-3.84 (*m*, 2H, OCH*H*), 2.69-2.59 (*m*, 4H, CH_2CH_2), 1.77 (*d*, 3H, *J* = 6.9 Hz, CH_3), 1.14 (*t*, 3H, *J* = 7.1 Hz, 2xCH_3). *Z*-isomer: 7.31-7.21 (*m*, 5H, H_{ar}), 5.72 (*t*, 1H, *J* = 7.5 Hz, H_{olef}), 4.62 (*s*, 2H, CH_2Ph), 4.13-4.04 (*m*, 2H, OC*H*H), 3.94-3.84 (*m*, 2H, OCH*H*), 2.69-2.59 (*m*, 4H, CH_2CH_2), 1.69 (*d*, 3H, *J* = 7.5 Hz, CH_3), 1.18 (*t*, 3H, *J* = 7.1 Hz, 2xCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): *E*-isomer: 172.4 (CO), 167.6 (2xCO), 137.6 (C_{olef}), 129.9 (C_{ar}), 128.0 (2xCH_{ar}), 127.1 (2xCH_{ar}), 126.7 (CH_{ar}), 124.3 (CH_{olef}), 76.4 (C), 62.3 (2xCH_2), 50.4 (CH_2), 32.0 (CH_2), 22.2 (CH_2), 13.7 (2xCH_3), 13.7 (CH_2). *Z*-isomer: 172.6 (CO), 167.0 (2xCO), 137.3 (C_{olef}), 132.5 (C_{ar}), 127.9 (2xCH_{ar}), 127.2 (2xCH_{ar}), 126.7 (CH_{ar}), 126.3 (CH_{olef}), 73.8 (C), 62.3 (2xCH_2), 49.3 (CH_2), 32.7 (CH_2), 30.7 (CH_2), 14.7 (CH_2), 13.7 (2xCH_3). IR (film): 3063m, 3030m, 2982m, 2938m, 1733s (C=O, ester), 1606s (C=O, amide). MS (ESI+): 360.2 (71, $[M+H]^+$), 382.2 (77, $[M+Na]^+$), 719.4 (100, $[2M+H]^+$), 741.3 (100, $[2M+Na]^+$). HRMS (ESI): calculated for $C_{20}H_{25}NNaO_5$ ($[M+Na]^+$) 382.1625, found 382.1625.

References

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