

MATERIAL AND METHODS

Materials

Instrumentation

The following analytical methods were used throughout this work, unless otherwise indicated.

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba MOD 1106 Elemental Analyser. Mass spectra (EI and FAB) were obtained using a VG-Autospec operating at 70 eV. Electrospray (ES) mass spectra were obtained on a LCT Micromass (TOF). Accurate molecular masses were determined at Leeds using perfluorotributylamine or polyethylenimine as an internal standard or obtained from the EPSRC Swansea Mass Spectroscopy Service. IR spectra were recorded on a Nicolet Magna FT-IR 560 spectrometer. To prepare samples for IR, a small amount of sample was dissolved in dichloromethane, transferred onto a germanium plate and left to dry. Optical rotation was recorded on a AA100 polarimeter.

Nuclear magnetic resonance spectra were recorded at 250 MHz on a Bruker AC 250 instrument or at 500 MHz on a Bruker DRX 500 instrument. Deuteriochloroform was used as the solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts are given in part per million (δ) downfield from tetramethylsilane (TMS) and coupling constants are given in Hertz (Hz). Enantioselectivities were determined by HPLC using chiral stationary phase (Daicel Chiralcel OD column, 250 x 4.6 mm) with 1 ml/min flow rate (solvent system hexane/IPA; 80/20), and monitored by UV fluorescence at 230 nm.

Chromatographic system

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F₂₅₄ plates (Merck) and the chromatograms were

visualized under a 254 nm UV lamp and/or by spraying with a solution of vanillin (3% in ethanol with 3% sulfuric acid) followed by heating.

Flash column chromatography was performed according to the method of Still and co-workers (1978) using silica gel 60 (Merck 9385, 230-400 mesh).

Column chromatography was performed on silica gel 60 (70-230 mesh, Merck) and the column was packed by slurry method.

Chemical reagents

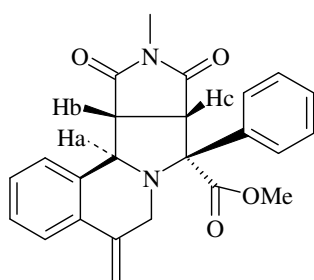
Solvents and reagents used for synthesis were obtained from commercial sources and used directly without purification unless noted. All reagents and solvents were purified according to literature procedures. The term ether refers to diethyl ether and petroleum ether is the fraction with boiling point 40-60 °C. Dry tetrahydrofuran (THF) was freshly distilled under N₂ from sodium with benzophenone ketyl as an indicator.

Experimental details of the reactions that failed have not been reported, although they are discussed.

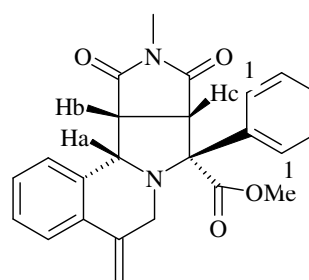
Methods

Amino acid methyl ester hydrochloride (1.2 mmol) was mixed with 2-iodobenzaldehyde (232 mg, 1.0 mmol), *N*-methylmaleimide (155 mg, 1.4 mmol), Pd₂dba₃ (23 mg, 2.5 mol%), TFP (23 mg, 10 mol%) and Cs₂CO₃ (4 mmol, 1.4g.) in toluene (15 ml) in a Schlenk tube. The mixture was solidified (liq. N₂) and degassed (two freeze, pump, and thaw cycles) before addition of allene (1 bar). It was then heated at 100 °C for 24 h. The mixture was allowed to cool to room temperature and excess allene vented. Then the reaction mixture was filtered through celite, the solvent was evaporated under vacuum and the resulting crude product was purified by flash column chromatography.

Methyl (8*S*,8*aS*,11*R*,11*bR*)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8*a*, 9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (126) and methyl (8*S*,8*aS*,11*R*,11*bS*)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (127)



(126)



(127)

According to the general procedure, phenyl glycine methyl ester hydrochloride (125) (242 mg, 1.2 mmol) was employed to give crude product. Purification by flash column chromatography eluting with ether afforded the product (126) (125 mg, 31%) and the product (127) (136 mg, 34%).

126 obtained as colourless needles, m.p. 244-246 °C

FTIR ν_{\max} (film), 2951, 1773, 1701, 1485, 1434, 1380, 1280 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, 1H, J 7.7 Hz, ArH), 7.80 (d, 1H, J 7.6 Hz, ArH), 7.63 (d, 2 x 1H, J 7.5 Hz, ArH), 7.33-7.46 (m, 5H, ArH), 5.73 and 5.05 (s, 2 x 1H, =CH₂), 4.28 (d, 1H, J 7.9 Hz, Ha), 3.81 (d, 1H, J 13.2 Hz, NCHH), 3.75 (s, 3H, OMe), 3.50 (dd, 1H, J 10.2 and 7.9 Hz, Hb), 3.43 (d, 1H, J 10.2 Hz, Hc), 3.14 (s, 3H, NMe), 3.11 (d, 1H, J 13.2 Hz, NCHH)

^{13}C NMR (75 MHz, CDCl_3) δ 176.6 (C=O), 175.9 (C=O), 169.1 (C=O), 132.2 (Cq), 138.9 (Cq), 137.1 (2 x Cq), 128.6 (2xCH), 128.0 (CH), 127.3 (CH), 127.1 (CH), 126.5 (2xCH), 123.6 (CH), 108.3 (CH₂), 63.0 (CH), 56.6 (CH), 52.2 (CH₂), 51.9 (CH₃), 49.8 (CH), 25.2 (CH₃)

m/z (ES, %) : 402.9 (M+1, 100).

Found; C, 71.60; H, 5.30; N, 7.10 $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$: C, 71.63; H, 5.51; N, 6.96%

n.O.e	Enhancement (%)		
	Ha	Hb	Hc
Irradiated proton			
Ha	-	-	-
Hb	2.68	-	6.98
Hc	-	4.28	3.22

127 obtained as colourless needles, m.p. 220-221 °C.

FTIR ν_{\max} (film) 3016, 2951, 2796, 1776, 1745, 1703, cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 7.52 (t, 2H, J 7.3 Hz, ArH), 7.37 (t, 2H, J 7.3 Hz, ArH), 7.29 (t, 1H, J 7.3 Hz, ArH), 7.22 (d, 2H, J 7.7 Hz, ArH, H1), 7.12 (t, 1H, J

According to the general procedure, alanine methyl ester hydrochloride (129) (167.5 mg, 1.2 mmol) was employed and the reaction was carried out at 110 °C for 24 h to give crude product. Purification by flash column chromatography eluting with ether afforded the product (139) (227 mg, 67%) as colourless needles, m.p. 214-215 °C.

FTIR ν_{\max} (film) 2991, 2950, 1739, 1700, 1435, 1383, 1248 cm^{-1}

^1H NMR (300 MHz, CDCl_3) δ 7.67 (d, 1H, J 7.7 Hz, ArH), 7.57 (d, 1H, J 7.7 Hz, ArH), 7.35-7.21 (m, 2H, ArH), 5.60 and 5.00 (s, 2 x 1H, =CH₂), 4.40 (d, 1H, J 7.2 Hz, Ha), 3.77 (s, 3H, OMe), 3.71 (t, 1H, J 7.2 Hz, Hb), 3.52 (d, 1H, J 11.8 Hz, CHHN), 3.22 (m, 2H, Hc and CHHN), 2.82 (s, 3H, NMe) 1.48 (s, 3H, Me).

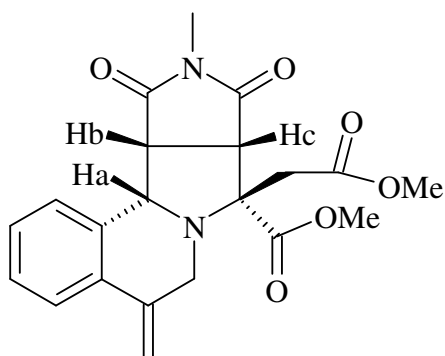
^{13}C NMR (75 MHz, CDCl_3) δ 176.0 (C=O), 175.0 (C=O), 172.1 (C=O), 139.1 (Cq), 132.6 (Cq), 132.5 (Cq), 128.8 (CH), 127.5 (CH), 127.3 (CH), 124.4 (CH), 109.1 (CH₂), 70.4 (C), 62.4 (CH), 54.8 (CH), 53.1 (CH), 51.1 (CH₃), 45.9 (CH₂), 25.6 (CH₃), 15.0 (CH₃).

m/z (ES; %): 340.8 (M+1, 100).

Found; C, 67.10; H, 5.96; N, 8.35 $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4$: C, 67.05; H, 5.92; N, 8.23%.

n.O.e	Enhancement (%)			
	Ha	Hb	Hc	Me
Irradiated proton				
Ha	-	9.4	4.1	6.4
Hb	8.4	-	11.2	2.1
Me	5.1	1.1	6.4	-

Methyl (8*S*,8*aS*,11*R*,11*bS*)-8-(2-methoxy-2-oxoethyl)-10-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline -8-carboxylate (140)



(140)

According to the general procedure, aspartic acid methyl ester hydrochloride (130) (237 mg, 1.2 mmol) was employed to give crude product. Purification by flash column chromatography eluting with ether afforded the product (140) (227 mg, 57%) as pale yellow needles, m.p. 95-96 °C.

FTIR ν_{\max} (film) 2952, 1776, 1735, 1703, 1436, cm^{-1}

^1H NMR (300 MHz, CDCl_3): 7.64 (d, 1H, J 6.7 Hz, ArH), 7.54 (d, 1H, J 7.2 Hz, ArH), 7.36-7.22 (m, 2H, ArH), 5.57 and 5.01 (s, 2 x 1H, =CH₂), 4.45 (d, 1H, J 7.7 Hz, Ha), 3.88 (d, 1H, J 8.19 Hz, CHHN), 3.80 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.70 (m, 2H, Hb and CHHN), 3.18 (d, 1H, J 12.3 Hz, Hc), 2.93 and 2.84 (d, 2 x 1H, J 15.8 Hz, CH₂), 2.82 (s, 3H, NMe).

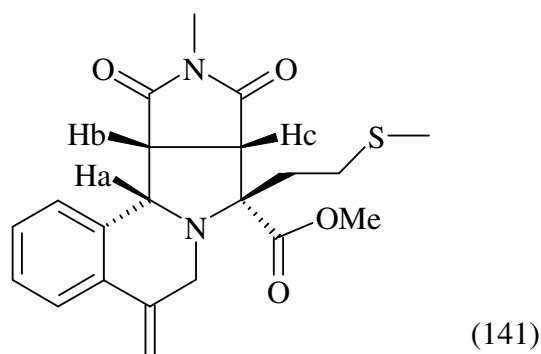
^{13}C NMR (75 MHz, CDCl_3) δ 170.8 (2 x C=O), 169.8 (C=O), 166.9 (C=O), 133.9 (Cq), 127.4 (Cq), 127.3 (Cq), 123.6 (CH), 122.6 (CH), 122.0 (CH), 119.1 (CH), 103.8 (CH₂), 65.2 (Cq), 57.2 (CH), 49.5 (2x CH₃), 47.9 (CH₂), 45.9 (CH), 40.7 (CH), 20.4 (CH₃), 9.8 (CH₂).

m/z (ES, %): 398.8 (M+1, 100).

Found; C, 63.35; H, 5.60; N, 7.10 C₂₁H₂₂N₂O₆: C, 63.31; H, 5.57; N, 7.03%.

n.O.e	Enhancement (%)			
	Ha	Hb	Hc	CH ₂ CO ₂ Me
Irradiated proton	Ha	Hb	Hc	CH ₂ CO ₂ Me
Ha	-	10.0	3.4	8.6
Hc	4.9	26.7	-	0.3
CH ₂ CO ₂ Me	6.6	2.1	2.0	-

Methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-8-[(methylthio)methyl]-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (141)



According to the general procedure, methionine methyl ester hydrochloride (131) (240 mg, 1.2 mmol) was employed and the reaction was carried out at 100 °C for 24 h to give crude product. Purification by flash column chromatography eluting with ether afforded the product (141) (216 mg, 56%) as yellow plates, m.p. 84-85 °C.

FTIR ν_{\max} (film) 3056, 2951, 1775, 1732, 1702, 1603, 1435, 1382 cm⁻¹

¹H NMR (300 MHz, acetone-d₆) δ 7.67 (d, 1H, *J* 7.2 Hz, ArH), 7.55 (d, 1H, *J* 7.7 Hz, ArH), 7.29- 7.20 (m, 2H, ArH), 5.56 and 4.96 (s, 2 x 1H, =CH₂), 4.61 (d, 1H, *J* 6.7 Hz, Ha), 3.96 (t, 1H, *J* 6.7, Hb), 3.67 (s, 3H, OMe), 3.51(d, 1H, *J* 6.7 Hz, Hc), 3.42 (d, 1H, *J* 12 Hz, CHHN), 2.91 (m, 2H, CH₂S), 2.69 (s, 3H, NMe), 2.38 (m, 1H, CHHN), 2.2-2.05 (m, 2H, CH₂CH₂S), 2.16 (s, 3H, SMe).

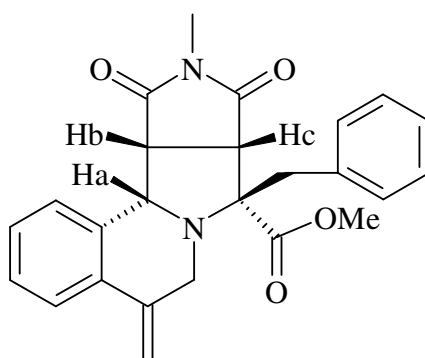
^{13}C NMR (75 MHz, acetone- d_6): 177.0 (C=O), 176.0 (C=O), 172.3 (C=O), 141.2 (Cq), 134.7 (Cq), 133.5 (Cq), 130.3 (CH), 128.0 (CH), 127.8 (CH), 125.0 (CH), 108.4 (CH₂), 74.0 (CH), 62.9 (CH), 61.0 (Cq), 53.3 (CH₃), 52.9 (CH), 52.1 (CH₂), 47.4 (CH₂), 31.8 (CH₂), 29.4 (CH₃), 25.4 (CH₃).

m/z (ES, %): 400.8 (M+1, 100).

Found; C, 62.80; H, 6.10; N, 6.83 C₂₁H₂₄N₂O₄S: C, 62.98; H, 6.04; N, 6.99%

n.O.e	Enhancement (%)		
	Ha	Hb	CH ₂ S
Irradiated proton			
Ha	-	8.4	7.3
Hb	7.5	-	6.5
CH ₂ S	2.4	3.7	-

Methyl (8*S*,8*aS*,11*R*,11*bS*)-8-benzyl-10-methyl-5-methylene-9,11-dioxo-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (142)



(142)

According to the general procedure, phenyl alanine methyl ester hydrochloride (132) (259 mg, 1.2 mmol) was employed and the reaction mixture was

carried out at 100 °C for 24 h to give crude product. Purification by flash column chromatography eluting with ether afforded the product **142** (230 mg, 55%) as pale yellow plates, m.p. 173-174.2 °C.

FTIR ν_{\max} (film) 3062, 3027, 2951, 1775, 1736, 1703, 1602, 1495, 1435, 1287 cm^{-1}

^1H NMR (300 MHz, CDCl_3) δ 7.59 (d, 1H, J 8.2 Hz, ArH), 7.55 (d, 1H, J 7.9 Hz, ArH), 7.35-7.20 (m, 7H, ArH), 5.45 and 4.90 (s, 2 x 1H, =CH₂), 4.7 (d, 1H, J 7.7 Hz, Ha), 3.84 (s, 3H, OMe), 3.62 (t, 1H, J 7.7 Hz, Hb), 3.52 (d, 1H, J 12.2 Hz, CHHN), 3.38 (s, 2H, CH₂Ph), 3.37 (d, 1H, J 7.7 Hz, Hc), 3.15 (d, 1H, J 12.2 Hz, CHHN), 2.77 (s, 3H, NMe).

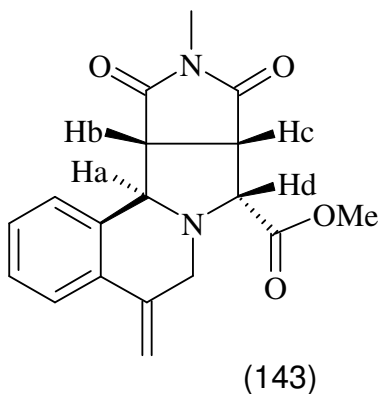
^{13}C NMR (75 MHz, CDCl_3) δ 176.2 (C=O), 175.1 (C=O), 172.2 (C=O), 139.5 (Cq), 137.6 (Cq), 133.2 (Cq), 132.5 (Cq), 131.0 (CH), 130.0 (CH), 129.3 (CH), 129.2 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 124.7 (CH), 108.7 (CH₂), 73.8 (C), 62.5 (CH), 53.1 (CH₂), 53.1 (CH), 51.2 (CH₃), 46.5 (CH₂), 37.4 (CH), 25.7 (CH₃).

m/z (ES, %): 416.9 (M+1, 100).

Found; C, 71.90; H, 5.96; N, 6.51 $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_4$: C, 72.10; H, 5.81; N, 6.73%

n.O.e	Enhancement (%)		
	Ha	Hb	Hc and CH ₂ Ph
Irradiated proton	Ha	Hb	Hc and CH ₂ Ph
Ha	-	11.0	7.1
Hb	8.2	-	8.5
Hc and CH ₂ Ph	3.90	4.7	-

Methyl (8S,8aS,11R,11bR)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (143)



According to the general procedure, glycine methyl ester hydrochloride (138) (150 mg, 1.2 mmol) was employed and the reaction was carried out at 110 °C for 48 h to give crude product. Purification by flash column chromatography eluting with 1:3 v/v hexane: ether afforded the inseparable 3:1 mixture product (88 mg, 27%) of (143) and (144) as a colourless gum.

FTIR ν_{\max} (film) 3041, 2952, 2854, 1778, 1750, 1700, 1481

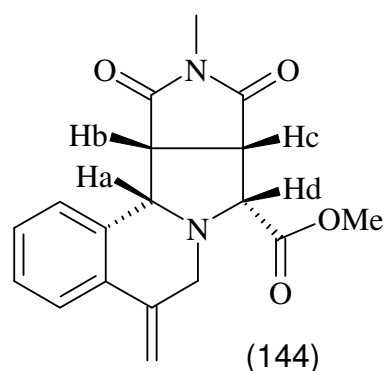
^1H NMR (300 MHz, CDCl_3): a major product **143**: 7.64 (d, 1H, J 7.8 Hz, ArH), 7.52 (d, 1H, J 7.6 Hz, ArH), 7.34-7.22 (m, 2H, ArH), 5.56 and 4.98 (s, 2 x 1H, =CH₂), 4.61 (d, 1H, J 7.5 Hz, Ha), 4.24 (bs, 1H, Hd), 3.80 (dd, 1H, J 9.7 and 7.5 Hz, Hb), 3.78 (s, 3H, OMe), 3.66 (d, 1H, J 12.5 Hz, CHHN), 3.62 (d, 1H, J 9.7 Hz, Hc), 3.46 (d, 1H, J 12.5 Hz, CHHN), 2.84 (s, 3H, NMe).

m/z (ES, %): 326.9 (M+1, 100).

HRMS (ES+) Found MH^+ , 327.1338 $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4$ requires MH^+ , 327.1345.

n.O.e	Enhancement (%)			
	Ha	Hb	Hc	Hd
Ha	-	15.7	-	-
Hc	-	7.4	-	3.21
Hd	-	3.4	2.59	-

Methyl (8*S*,8*aS*,11*R*,11*bS*)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8*a*,9,10,11,11*a*,11*b*-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (144)



According to the general procedure, glycine methyl ester hydrochloride (138) (150 mg, 1.2 mmol) was employed and the reaction was carried out at 100 °C for 12 h to give crude product. Purification by flash column chromatography eluting with 1:3 v/v hexane: ether afforded the product **144** (222 mg, 68%) as colourless needles, m.p. 175-176 °C.

FTIR ν_{\max} (film) 3056, 2952, 2854, 1778, 1751, 1703, 1481, 1436, 1385 cm^{-1}

^1H NMR (300 MHz, CDCl_3) δ 7.59 (d, 1H, J 7.8 Hz, ArH), 7.38-7.26 (m, 3H, ArH), 5.70 (s, 1H, C=CHH), 5.60 (bs, 1H, Hd), 5.0 (s, 1H, C=CHH), 3.88-3.84 (m, 2H, Ha and CHHN), 3.84 (s, 3H, OMe), 3.67(d, 1H, J 7.2 Hz, Hb), 3.48 (m, 2H, J 4.6 Hz, Hc and CHHN), 3.05 (s, 3H, NMe).

^{13}C NMR (75 MHz, CDCl_3) δ 177.6 (C=O), 176.4 (C=O), 170.1 (C=O), 135.2 (Cq), 134.1 (Cq), 133.1 (Cq), 129.7 (CH), 127.8 (CH), 124.4 (2 x CH), 112.6 (CH_2), 66.1 (CH), 62.3 (CH), 52.8 (CH_3), 51.6 (2x CH), 47.5 (CH_2), 26.0 (CH_3).

m/z (ES, %): 326.9 (M^+ 1, 100).

Found; C, 66.14; H, 5.62; N, 8.6 $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$: C, 66.25; H, 5.56; N, 8.58%.

n.O.e	Enhancement (%)			
Irradiated proton	Ha	Hb	Hc	Hd
Ha	-	15.7	1.1	1.4
Hb	31.7	-	-	8.6
Hc	1.2	1.0	-	3.21
Hd	0.4	3.4	2.59	-