A Convenient Protocol for the Alkylidenation of Lactams

Mark C. Elliott,* Stuart V. Wordingham

School of Chemistry, Cardiff University, Park Place, Cardiff CF10 3AT, UK
Fax +44(29)20874030; E-mail: elliottmc@cardiff.ac.uk

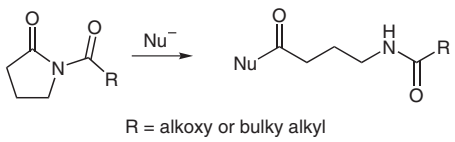
Received 22 September 2005; revised 15 November 2005

Dedicated to Dr. M. J. E. Hewlins on the occasion of his retirement

Abstract: A convenient two-step preparation of alkylidenepyrrolidines is reported.

Key words: heterocycles, enamines, imides, enolates, aldol reactions

Alkylidenepyrrolidines have long been used as synthetic intermediates, particularly in the synthesis of pyrrolidines and porphyrins.[1] These compounds are generally prepared by reaction of a thioamide with a α-bromocarbonyl compound in a reaction commonly known as the Eschenmoser sulfide contraction.[2] The O-alkylation of lactams followed by treatment with a malonate-type nucleophile also gives the same compounds,[3] although we have found this method to be somewhat capricious. During the course of studies directed towards the batzelladine alkaloids,[4] we required a broad range of alkylidenepyrrolidines, and therefore sought a more convenient method for their preparation. It is well known that imides and carbamates derived from γ-lactams can be selectively attacked at the lactam carbonyl by a range of nucleophiles, including Grignard reagents,[5,6] other organometallics,[7,8] heteronucleophiles[9] and stabilised anions[10–13] (Equation 1). The products of this reaction have been cyclised to the corresponding pyrrolines and pyrrolidines in a number of instances,[6,8,12] but we are aware of only a single example of the application of this general approach to alkylidenepyrrolidine synthesis, this being the preparation of sulfonyl alkylidenepyrrolidines.[14,15] We have therefore undertaken a study of this approach, and now report an efficient and convenient two-step preparation of alkylidenepyrrolidines which can be carried out on a multi-gram scale.



Equation 1

Lactams **1**,[16] **2**[17] and **3**[18] were prepared according to literature procedures. Compounds **1** and **2** underwent ready reaction with ketone and ester enolates to provide a range of compounds **4** and **5** as shown in Equation 2 (Table 1). As expected, the β-keto esters existed solely in the keto form, while the 1,3-diketones showed significant ($R^2 = CH_3$) to total ($R^2 = Ph$) enolisation. In all cases with ketone and ester enolates, the reactions were clean and high-yielding, and in many instances the crude products were essentially pure.

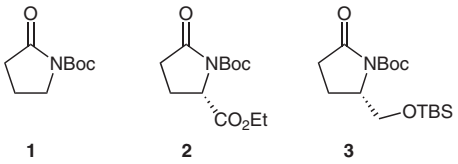
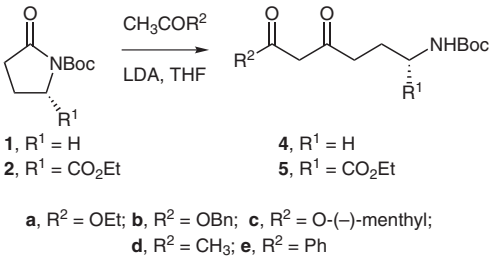


Figure 1 Lactams **1**–**3**



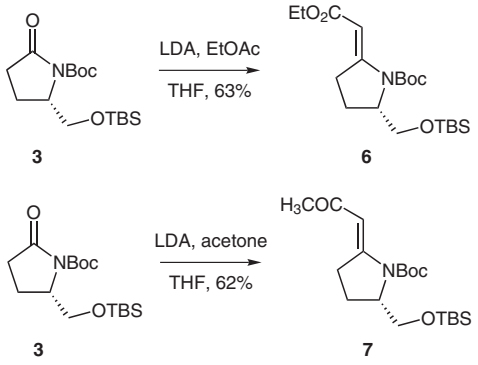
Equation 2

Table 1 Compounds **4** and **5** Prepared

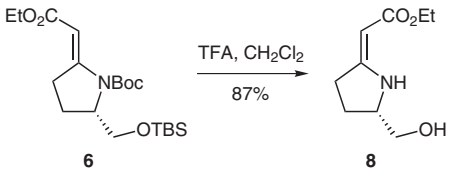
Compound	R^1	R^2	Yield (%)
4a	H	OEt	88
4b	H	OBn	68
4c	H	O-(–)-menthyl	84
4d	H	Me	74
4e	H	Ph	75
5a	CO_2Et	OEt	78
5b	CO_2Et	OBn	67
5c	CO_2Et	O-(–)-menthyl	71
5d	CO_2Et	Me	72
5e	CO_2Et	Ph	74

SYNTHESIS 2006, No. 7, pp 1162–1170
Advanced online publication: 14.03.2006
DOI: 10.1055/s-2006-926390; Art ID: P15405SS

In reactions of compound **3**, the desired products could only be observed in the ^{1}H NMR spectrum of the crude reaction mixture, and upon standing overnight or rapid chromatography on silica gel, only the cyclised compounds **6** and **7** were isolated (Scheme 1). Compounds **4** and **5** underwent similar cyclisation, but at a much slower rate (several days standing in $CDCl_3$). Treatment of compound **6** with trifluoroacetic acid in dichloromethane removed both the nitrogen and oxygen protecting groups to give compound **8** in excellent yield (Scheme 2). The double-bond geometries of **6**–**8** seem likely, although these are not trivial to determine (see below).

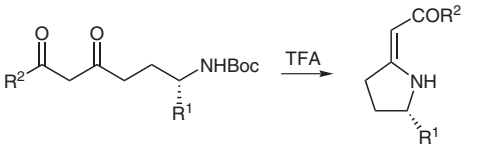


Scheme 1



Scheme 2

Cyclisation reactions of compounds **4** and **5** were investigated next. These occurred smoothly under similar conditions to the formation of compound **8** (Equation 3). The results of these reactions are summarised in Table 2.



4, R^1 = H
5, R^1 = CO_2Et

9, R^1 = H
10, R^1 = CO_2Et

a, R^2 = OEt; **b**, R^2 = OBn; **c**, R^2 = O-(–)-menthyl;
d, R^2 = CH_3; **e**, R^2 = Ph

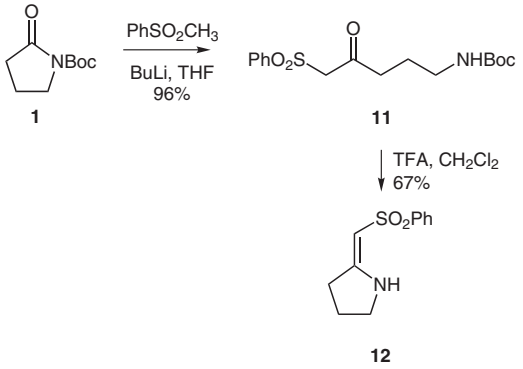
Equation 3

It has previously been reported that ring-opening reactions of substrate **2** proceed without racemisation.[10,11] We were able to confirm that this is indeed the case by use of racemic and optically pure menthyl acetates in the above reaction. Comparison of the ^{13}C NMR data clearly showed the presence of two diastereoisomers from the racemic menthyl acetate, and only one from optically pure menthyl acetate in both compounds **5c** and **10c**. We would therefore estimate the diastereomeric purity of compounds **5c** and **10c** to be >95%, and see no reason why the other compounds **10** should show any greater loss of stereochemical integrity.

Table 2 Compounds **9** and **10** Prepared

Compound	R^1	R^2	Yield %)
9a	H	OEt	78
9b	H	OBn	86
9c	H	O-(–)-menthyl	80
9d	H	Me	85
9e	H	Ph	74
10a	CO_2Et	OEt	82
10b	CO_2Et	OBn	72
10c	CO_2Et	O-(–)-menthyl	75
10d	CO_2Et	Me	55
10e	CO_2Et	Ph	44

Formation of sulfone **12** was carried out under the present reaction conditions (Scheme 3), and the overall yield for the two steps was found to be comparable for the previous formation of this compound.[14]



Scheme 3

The double-bond geometry in alkylidenepyrrolidines such as **9** and **10** is not trivial to determine. Since both the NH and alkene CH (enamine) protons are exchangeable, the expected strong NOE enhancement between these protons is observed, and should not be used as an indication of double-bond geometry. During the course of the present study, we have only observed small NOE enhancements between the alkene CH and the allylic methylene group on the ring which would support the expected *Z* double-bond geometry.[19] For steric reasons, compound **6** presumably possesses the *E* double-bond geometry shown. The ^{1}H NMR spectrum of this compound shows the 4-CH_2 of the pyrrolidine ring to be significantly deshielded compared to compound **8**, which we assume to have the *Z*-geometry.

This chemical shift has been attributed to anisotropic effects,[20] although since the only way to assure the *E* double-bond geometry is to introduce a substitutent onto the nitrogen atom, it is almost impossible to compare data for both isomers of a single compound.[21] The N–H stretches in the infrared spectra of compounds **9** and **10** show that the esters **9a–c** and **10a–c** are in the region of 3370 cm^{-1}, while the ketones **9d**,**e** and **10d**,**e** are all below 3300 cm^{-1}. The proton chemical shifts for the NH protons in this latter group of compounds are significantly deshielded with respect to the former.[22] From this we can conclude that the same *Z* double-bond geometry is formed in all cases.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^1H NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 micron.

Ethyl 6-*tert*-Butoxycarbonylamino-3-oxohexanoate (4a)

A solution of lithium diisopropylamide (13.5 mL, 2 M in heptane, 27 mmol) in THF (100 mL) was cooled to –78 °C. EtOAc (2.58 mL, 27 mmol) in THF (3 mL) was added dropwise over 30 min, and the solution allowed to stir for a further 30 min. *N*-*tert*-Butoxycarbonylpyrrolidin-2-one (**1**; 5.0 g, 27 mmol) in THF (5 mL) was added over 30 min at –78 °C, and the solution warmed to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl solution (100 mL) was added and the organic material extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash column chromatography (eluent 2:1 hexane–EtOAc) gave the title compound (6.46 g, 88%) as a pale-yellow oil.

IR (neat): 3380, 2977, 2925, 1739, 1709, 1521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.60 (br s, 1 H, NH), 4.12 (q, *J* = 7.1 Hz, 2 H, CH_2O), 3.41 (s, 2 H, $COCH_2CO$), 3.06 (app q, *J* = 6.5 Hz, 2 H, CH_2NHBoc), 2.53 (t, *J* = 7.1 Hz, 2 H, $COCH_2$), 1.72 (app quintet, *J* = 6.9 Hz, 2 H, $CH_2CH_2CH_2$), 1.37 [s, 9 H, $C(CH_3)_3$], 1.21 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7 (C=O), 168.3 (C=O), 157.0 (C=O), 79.7 [$OC(CH_3)_3$], 61.8 (OCH_2), 49.6 (NCH_2), 40.2 ($COCH_2CO$), 39.9 ($COCH_2CH_2$), 28.6 [$C(CH_3)_3$], 24.0 (CH_2CH_2N), 14.2 (OCH_2CH_3).

MS-ES: *m*/*z* (%) = 296 (M + Na, 83), 240 (7), 156 (100), 128 (16).

HRMS-ES: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{23}NO_5$ + Na: 296.1474; found: 296.1473.

Benzyl 6-*tert*-Butoxycarbonylamino-3-oxohexanoate (4b)

A solution of lithium diisopropylamide (2.7 mL, 2 M in heptane, 5.4 mmol) in THF (40 mL) was cooled to –78 °C. Benzyl acetate (810 mg, 5.4 mmol) in THF (3 mL) was added over 30 min. After stirring for 30 min at –78 °C, *N*-*tert*-butoxycarbonylpyrrolidin-2-one (**1**; 1.0 g, 5.4 mmol) in THF (8 mL) was added over 30 min at –78 °C, and the solution allowed to warm to 25 °C and stirred for 18 h. Sat. aq NH_4Cl (100 mL) was added and the organic material extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Purification by flash column chromatography (eluent: 5:1 hexane–EtOAc) gave the title compound (1.2 g, 68%) as a pale oil.

IR (neat): 3402, 2976, 2925, 1739, 1714, 1519, 1167, 751, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H_{arom}), 5.10 (s, 2 H, OCH_2), 4.50 (br s, 1 H, NH), 3.42 (s, 2 H, $COCH_2CO$), 3.01 (app q, *J* = 6.4 Hz, CH_2N), 2.50 (t, *J* = 7.1 Hz, 2 H, CH_2CO), 1.68 (app quintet, *J* = 6.8 Hz, 2 H, $CH_2CH_2CH_2$), 1.37 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.7 (ketone C=O), 167.1 (ester C=O), 156.1 (carbamate C=O), 135.2 (C_{arom}), 128.7 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 79.3 [$(CH_3)_3CO$], 67.2 (CH_2O), 49.2 (CH_2N), 45.0 ($COCH_2CO$), 39.6 ($COCH_2$), 28.4 [$C(CH_3)_3$], 23.8 (CH_2CH_2N).

MS-ES: *m*/*z* (%) = 358 (M + Na, 62), 218 (100).

HRMS-ES: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_5$ + Na: 358.1630; found: 358.1623.

(–)-Menthyl 6-*tert*-Butoxycarbonylamino-3-oxohexanoate (4c)

A solution of lithium diisopropylamide (1.5 mL, 2 M in heptane, 3 mmol) in THF (10 mL) was cooled to –78 °C. (–)-Menthyl acetate (595 mg, 3 mmol) in THF (3 mL) was added over 30 min. After stirring for 30 min at –78 °C, *N*-*tert*-butoxycarbonylpyrrolidin-2-one (**1**; 555 mg, 3 mmol) in THF (5 mL) was added over 30 min at –78 °C, and the solution warmed to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow crystalline solid which was recrystallised from hexane–Et_2O to give the title compound (965 mg, 84%) as an off-white crystalline solid; mp 88–89 °C.

IR ($CHCl_3$): 3398, 2958, 1735, 1715, 1170 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.65 (app dt, *J* = 4.4, 10.9 Hz, 1 H, menthyl 1-H), 4.59–4.52 (br s, 1 H, NH), 3.37 and 3.35 (AB quartet, *J* = 15.5 Hz, 2 H, $COCH_2CO$), 3.05 (app q, *J* = 6.3 Hz, 2 H, CH_2N), 2.52 (t, *J* = 7.1 Hz, 2 H, CH_2CO), 1.98–1.92 (m, 1 H, menthyl 6-H_{eq}), 1.82–1.75 [app doubled septet, *J* = 2.7, 7.0 Hz, 1 H, $CH(CH_3)_2$], 1.72 (app quintet, *J* = 6.9 Hz, 2 H, $CH_2CH_2CH_2$), 1.64–1.58 (m, 2 H, menthyl 3-H_{eq} and 4-H_{eq}), 1.48–1.40 (m, 1 H, menthyl 5-H_{ax}), 1.37 [s, 9 H, $C(CH_3)_3$], 1.35–1.27 (m, 1 H, menthyl 2-H_{ax}), 1.03–0.96 (m, 1 H, menthyl 3-H_{ax}), 0.92 (app q, *J* = 11.7 Hz, 1 H, menthyl 4-H_{ax}), 0.84 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.82 (d, *J* = 7.1 Hz, 3 H, CH_3), 0.82–0.77 (m, 1 H, menthyl 4-H_{ax}), 0.70 (d, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5 (ketone C=O), 166.9 (ester C=O), 156.1 (carbamate C=O), 79.2 (C–O), 75.5 (menthyl 1-CH), 49.6 ($COCH_2CO$), 46.8 (menthyl 2-CH), 40.7 (menthyl 6-CH_2), 40.0 (CH_2), 39.7 (CH_2), 34.1 (menthyl 4-CH_2), 31.4 (menthyl 5-CH), 28.4 [$(CH_3)_3CO$], 26.1 (CH), 23.8 (menthyl 3-CH_2), 23.2 (CH_2), 22.0 (CH_3), 20.7 (CH_3), 16.1 (CH_3).

MS-ES: *m*/*z* (%) = 406 (M + Na, 100), 266 (73), 128 (32).

HRMS-ES: *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{37}NO_5$ + Na: 406.2569; found: 406.2585.

***N*-*tert*-Butoxycarbonyl-4,6-dioxoheptylamine (4d)**

A solution of lithium diisopropylamide (1.5 mL, 2 M in heptane, 3 mmol) in THF (10 mL) was cooled to –78 °C. Acetone (174 mg, 3 mmol) in THF (3 mL) was added over 30 min. After stirring for 30 min at –78 °C, *N*-*tert*-butoxycarbonylpyrrolidin-2-one (**1**; 555 mg, 3 mmol) in THF (5 mL) was added over 30 min at –78 °C, and the solution warmed to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 50

mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (535 mg, 74%) as a colourless oil (5:1 mixture of enol and keto tautomers).

IR (CH_2Cl_2): 3357, 2976, 1703, 1619, 1170 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (enol tautomer) = 5.44 (s, 1 H, enol CH), 4.58 (br s, 1 H, NH), 3.09 (app q, *J* = 6.5 Hz, 2 H, CH_2N), 2.25 (t, *J* = 7.3 Hz, $COCH_2$), 1.98 (s, 3 H, CH_3), 1.73 (app quintet, *J* = 7.5 Hz, 2 H, CH_2), 1.37 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ (enol tautomer) = 194.0 (C=O), 190.7 (enol C–O), 156.0 (C=O), 100.0 (enol CH), 79.3 (C–O), 40.0 (CH_2N), 35.7 (CH_2), 28.4 [$C(CH_3)_3$], 25.9 (CH_2), 24.8 (CH_3).

MS-ES: *m*/*z* (%) = 266 (M + Na, 100), 127 (28).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{21}NO_4$ + Na: 266.1368; found: 266.1355.

N-*tert*-Butoxycarbonyl-4,6-dioxo-6-phenylhexylamine (4e)

A solution of lithium diisopropylamide (2.8 mL, 2 M solution in heptane, 5.6 mmol) in THF (10 mL) was cooled to –78 °C. Acetophenone (0.67 mL, 5.6 mmol) in THF (2 mL) was added over 20 min. After stirring for 25 min at –78 °C, *N*-*tert*-butoxycarbonylpyrrolidin-2-one (**1**; 1.0 g, 5.4 mmol) in THF (5 mL) was added over 30 min at –78 °C and the solution warmed to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give an oily solid which was recrystallised from EtOAc–hexane to give the title compound (1.23 g, 75%), as a off-white crystalline solid existing exclusively as the enol tautomer; mp 72–73 °C.

IR ($CHCl_3$): 3360, 2975, 2929, 1702, 1601, 1169 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.3 Hz, 2 H_{arom}), 7.43 (t, *J* = 7.3 Hz, 1 H_{arom}), 7.34 (app t, *J* = 7.4 Hz, 2 H_{arom}), 6.12 (s, 1 H, enol CH), 4.60 (br s, 1 H, NH), 3.11 (app q, *J* = 6.5 Hz, 2 H, CH_2N), 2.40 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 1.81 (app quintet, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_2$), 1.35 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.5 (ketone C=O), 182.9 (enol C–O), 156.0 (carbamate C=O), 134.8 (C_{arom}), 132.3 (CH_{arom}), 128.6 (CH_{arom}), 127.0 (CH_{arom}), 96.2 (enol CH), 78.9 [$(CH_3)_3CO$], 40.1 (CH_2N), 36.6 (CH_2), 28.4 [$C(CH_3)_3$], 26.0 (CH_2).

MS-ES: *m*/*z* (%) = 328 (M + Na, 89), 188 (100).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{23}NO_4$ + Na: 328.1525; found: 328.1499.

(2*S*)-2-*tert*-Butoxycarbonylamino-5-oxoheptanedioic Acid Diethyl Ester (5a)[11]

A solution of lithium diisopropylamide (3.9 mL, 2 M solution in heptane, 7.8 mmol) in THF (15 mL) was cooled to –78 °C. EtOAc (0.76 mL, 7.8 mmol) in THF (4 mL) was added over 25 min. After stirring for 20 min at –78 °C, compound **2** (2.0 g, 7.8 mmol) in THF (5 mL) was added over 30 min at –78 °C. The solution was then allowed to warm to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Filtration through a short plug of silica gel, eluting with EtOAc, gave the title compound (2.1 g, 78%), as a yellow oil.

IR (neat): 3368, 2979, 2934, 1741, 1713, 1512 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.07 (br d, *J* = 7.6 Hz, 1 H, NH), 4.23–4.05 (m, 1 H, C*H*NH), 4.12 (app q, *J* = 7.2 Hz, 4 H, CH_2O), 3.39 (s, 2 H, $COCH_2CO$), 2.70–2.50 (m, 2 H, m, CH_2CO), 2.16–2.05 (m, 1 H, one of CH_2CHN), 1.89–1.76 (m, 1 H, one of CH_2CHN), 1.39 [s, 9 H, $C(CH_3)_3$], 1.21 (app t, *J* = 7.2 Hz, 6 H, 2 CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7 (ketone C=O), 172.2 (ester C=O), 167.1 (ester C=O), 155.5 (carbamate C=O), 80.0 [$OC(CH_3)_3$], 61.6 (OCH_2), 61.5 (OCH_2), 52.7 (CHNH), 49.3 (CH_2NH), 38.8 (CH_2CO), 28.3 [$C(CH_3)_3$], 26.5 (CH_2) 14.2 (CH_2CH_3), 14.1 (CH_2CH_3).

MS-ES: *m*/*z* (%) = 384 (M + K, 34), 368 (M + Na, 100), 328 (17).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{27}NO_7$ + Na: 368.1685; found: 368.1659.

(2*S*)-2-*tert*-Butoxycarbonylamino-5-oxoheptanedioic Acid 1-Ethyl Ester 7-Benzyl Ester (5b)

A solution of lithium diisopropylamide (5.93 mL, 2 M in heptane, 11.87 mmol) in THF (60 mL) was cooled to –78 °C. Benzyl acetate (1.78 g, 11.87 mmol) in THF (10 mL) was added over 30 min. After stirring for 30 min at –78 °C, compound **2** (3.05 g, 11.87 mmol) in THF (10 mL) was added over 30 min at –78 °C. The solution was allowed to warm to 25 °C and stirred for 18 h. Sat. aq NH_4Cl (100 mL) was added and the organic material extracted into CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$), and the solvent removed in vacuo to give a yellow oil. Purification by flash column chromatography (eluent: 6:1 hexane–EtOAc) gave the title compound (3.1 g, 67%) as a pale oil.

IR (neat): 3384, 2977, 1740, 1710, 1368 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H_{arom}), 5.12 (s, 2 H, OCH_2), 5.05 (br d, *J* = 6.5 Hz, 1 H, NH), 4.22–4.09 (m, 3 H, C*H*NH and CH_2O), 3.45 (s, 2 H, $COCH_2CO$), 2.67–2.50 (m, 2 H, m, CH_2CO), 2.18–2.06 (m, 1 H, one of CH_2CHN), 1.90–1.78 (m, 1 H, one of CH_2CHN), 1.39 [s, 9 H, $C(CH_3)_3$], 1.22 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.4 (ketone C=O), 172.2 (ester C=O), 166.9 (ester C=O), 155.5 (carbamate C=O), 135.3 (C_{arom}), 128.7 (CH_{arom}), 128.5 (CH_{arom}), 128.4 (CH_{arom}), 80.0 [$OC(CH_3)_3$], 67.2 (OCH_2), 61.6 (OCH_2), 52.7 (CHNH), 49.2 (CH_2NH), 38.9 (CH_2CO), 28.3 [$C(CH_3)_3$], 26.5 (CH_2) 14.2 (CH_2CH_3).

MS-ES: *m*/*z* (%) = 430 (M + Na, 18), 352 (40), 290 (100).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}NO_7$ + Na: 430.1842; found: 430.1842.

(2*S*)-2-*tert*-Butoxycarbonylamino-5-oxoheptanedioic Acid 1-Ethyl Ester 7-(–)-Menthyl Ester (5c)

A solution of lithium diisopropylamide (1.5 mL, 2 M in heptane, 3 mmol) in THF (10 mL) was cooled to –78 °C. (–)-Menthyl acetate (1.23 g, 6.2 mmol) in THF (3 mL) was added over 30 min. After stirring for 30 min at –78 °C, compound **2** (1.6 g, 6.2 mmol) in THF (5 mL) was added over 30 min at –78 °C, and the solution warmed to 25 °C and allowed to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (2.0 g, 71%) as an off-white solid; mp 82–82.5 °C.

IR ($CHCl_3$): 3367, 2957, 1717 (v br), 1168 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.03 (br d, *J* = 6.3 Hz, 1 H, NH), 4.65 (app dt, *J* = 4.4, 10.9 Hz, 1 H, menthyl 1 H), 4.22–4.14 (m, 1 H, CHN), 4.11 (q, *J* = 7.1 Hz, 2 H, CH_2O), 3.38 and 3.35 (AB quartet, *J* = 15.5 Hz, 2 H, $COCH_2CO$), 2.65–2.50 (m, 2 H, CH_2CO), 1.98–1.92 (m, 1 H, menthyl 6-H_{eq}), 1.87–1.75 [m, 3 H, CH_2CH_2CO and $CH(CH_3)_2$], 1.64–1.58 (m, 2 H, menthyl 3-H_{eq} and 4-H_{eq}), 1.47–1.39 (m, 1 H, menthyl 5-H_{ax}), 1.37 [s, 9 H, $C(CH_3)_3$], 1.34–1.26 (m,

1 H, menthyl 2-H_{ax}), 1.21 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.03–0.93 (m, 1 H, menthyl 3-H_{ax}), 0.92 (app q, J = 11.8 Hz, 1 H, menthyl 6-H_{ax}), 0.84 (d, J = 6.6 Hz, 3 H, CH$_3$), 0.82 (d, J = 7.0 Hz, 3 H, CH$_3$), 0.81–0.76 (m, 1 H, menthyl 4-H_{ax}), 0.69 (d, J = 7.0 Hz, 3 H, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 201.7 (ketone C=O), 172.2 (ester C=O), 166.7 (ester C=O), 155.5 (carbamate C=O), 80.0 [(CH$_3$)$_3$*C*O], 75.6 (menthyl 1-CH), 61.2 (CH$_2$O), 52.8 (CHN), 49.6 (CH$_2$), 46.9 (menthyl 2-CH), 40.7 (menthyl 6-CH$_2$), 38.8 (CH$_2$), 34.2 (menthyl 4-CH$_2$), 31.4 (menthyl 5-CH), 28.3 [C(*C*H$_3$)$_3$], 26.6 (CH$_2$), 26.2 (CH), 23.3 (menthyl 3-CH$_2$), 22.0 (CH$_3$), 20.7 (CH$_3$), 16.2 (CH$_3$), 14.2 (CH$_3$).

MS-ES: *m*/*z* (%) = 494 (M + K, 13), 478 (M + Na, 24), 338 (100).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{41}NO_7$ + Na: 478.2781; found: 478.2795.

Ethyl (2*S*)-2-*tert*-Butoxycarbonylamino-5,7-dioxooctanoate (5d)

A solution of lithium diisopropylamide (2.5 mL, 2 M solution in heptane, 5 mmol) in THF (10 mL) was cooled to –78 °C. Acetone (0.31 mL, 4.3 mmol) in THF (2 mL) was added over 20 min. After stirring for 25 min at –78 °C, compound **2** (1.0 g, 3.9 mmol) in THF (5 mL) was added over 30 min at –78 °C. The solution was then allowed to warm to 25 °C and stirred for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash column chromatography (eluent: 4:1 hexane–Et_2O) to give the title compound (900 mg, 72%) as a yellow oil, existing as the enol tautomer.

IR ($CHCl_3$): 3372, 2979, 1712 (v br), 1164 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.41 (s, 1 H, enol CH), 5.04 (br d, J = 7.3 Hz, 1 H, NH), 4.23 (m, 1 H, C*H*NH), 4.13 (q, J = 7.1 Hz, 2 H, CH$_2$O), 2.35–2.29 (m, 2 H, CH_2CH$_2$), 2.15–2.05 (m, 1 H, one of CH_2CHN), 1.97 (s, 3 H, CH$_3$CO), 1.93–1.83 (m, 1 H, one of CH_2CHN), 1.37 [s, 9 H, C(CH$_3$)$_3$], 1.21 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 194.0 (C=O), 189.7 (enol C–O), 172.3 (C=O), 155.4 (C=O), 100.0 (enol CH), 79.9 (C–O), 61.5 (CH$_2$O), 53.1 (CHN), 34.5 (CH$_2$), 28.3 [C(*C*H$_3$)$_3$], 28.0 (CH$_2$), 24.4 (CH$_3$), 14.1 (CH$_3$).

MS-ES: *m*/*z* (%) = 354 (M + K, 62), 338 (100), 282 (21).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{25}NO_6$ + Na: 338.1580; found: 338.1569.

Ethyl (2*S*)-2-*tert*-Butoxycarbonylamino-5,7-dioxo-7-phenylheptanoate (5e)[11]

A solution of lithium diisopropylamide (2.5 mL, 2 M solution in heptane, 5 mmol) in THF (10 mL) was cooled to –78 °C. Acetophenone (0.53 mL, 4.3 mmol) in THF (2 mL) was added over 20 min. After stirring for 25 min at –78 °C, compound **2** (1.0 g, 3.9 mmol) in THF (5 mL) was added over 30 min at –78 °C. The solution was then allowed to warm to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a orange oil which was purified by flash column chromatography (eluent: 10:3 hexane–Et_2O) to give the title compound (1.1 g, 74%) as a yellow crystalline solid; mp 63–64 °C.

IR ($CHCl_3$): 3367, 2979, 1715 (v br), 1606, 1164 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.79 (app d, J = 7.2 Hz, 2 H$_{arom}$), 7.40 (app tt, J = 7.4, 1.2 Hz, 1 H$_{arom}$), 7.32 (app t, J = 7.6 Hz, 2 H$_{arom}$), 6.10 (s, 1 H, C*H*=CCOH), 5.11 (br d, J = 8.3 Hz, 1 H, NH), 4.28–4.22 (m, 1 H, C*H*NH), 4.09 (q, J = 7.2 Hz, 2 H, CH$_2$O), 2.52–2.41 (m, 2 H, CH_2CH$_2$), 2.19–2.10 (m, 1 H, one of CH_2CHN), 1.99–1.90 (m, 1 H, one of CH_2CHN), 1.35 [s, 9 H, C(CH$_3$)$_3$], 1.21 (t, J = 7.2 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 196.4 (Ph*C*=O), 182.0 (enol ether C–O), 172.3 (ester C=O), 155.5 (carbamate C=O), 134.4 (C$_{arom}$), 132.5 (CH$_{arom}$), 128.6 (CH$_{arom}$), 126.9 (CH$_{arom}$), 79.7 (Me$_3$*C*O), 61.4 (OCH$_2$), 53.1 (NCH), 35.4 (*C*H$_2$COH), 28.2 [C(*C*H$_3$)$_3$], 28.0 (*C*H$_2$CHN), 14.1 (CH$_3$).

MS-ES: *m*/*z* (%) = 416 (M + K, 75), 400 (M + Na, 100), 378 (M$^+$, 24).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{27}NO_6$ + Na: 400.1736; found: 400.1729.

(2*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-5-[(*E*)-1-ethoxycarbonylmethylidene]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (6)[23]

A solution of lithium diisopropylamide (0.25 mL, 2 M in heptane, 0.5 mmol) in THF (5 mL) was cooled to –78 °C. EtOAc (43 mg, 0.5 mmol) in THF (3 mL) was added over 20 min. After stirring for 25 min at –78 °C, compound **3** (164 mg, 0.5 mmol) in THF (2 mL) was added over 20 min at –78 °C. The solution was allowed to warm to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (20 mL) was added and the solution extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (2 × 15 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (123 mg, 63%) as a yellow oil.

IR (neat): 3368, 2955, 2857, 1739, 1709, 1501, 1471 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.42 (br s, 1 H, C=CH), 4.19–4.15 (m, 1 H, CHN), 4.08 (q, J = 7.1 Hz, 2 H, CH$_2$O), 3.68–3.62 (m, 2 H, CH$_2$OSi), 3.36 (app ddt, J = 18.4, 9.5, 1.5 Hz, 1 H, one of CH$_2$C=C), 2.96 (dddd, J = 18.4, 11.3, 9.1, 2.3 Hz, 1 H, one of CH$_2$C=C), 2.03–1.85 (m, 2 H, CH$_2$), 1.50 [s, 9 H, (CH$_3$)$_3$CO], 1.21 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 0.83 [s, 9 H, (CH$_3$)$_3$CSi], 0.00 [s, 3 H, one of (CH$_3$)$_2$Si], –0.02 [s, 3 H, one of (CH$_3$)$_2$Si].

^{13}C NMR (125 MHz, CDCl$_3$): δ = 169.0 (ester C=O), 158.4 (carbamate C=O), 151.6 (*C*=CH), 96.1 (C=*C*H), 82.1 [(CH$_3$)$_3$CO], 63.7 (CH$_2$OSi), 62.2 (CHN), 59.1 (CH$_2$O), 31.0 (CH$_2$), 28.3 [(*C*H$_3$)$_3$CO], 25.8 [(*C*H$_3$)$_3$CSi], 23.8 (CH$_2$), 18.2 (CSi), 14.5 (*C*H$_3$CH$_2$), –5.4 [one of (CH$_3$)$_2$Si], –5.5 [one of (CH$_3$)$_2$Si].

MS-ES: *m*/*z* (%) = 400 (MH$^+$, 9), 300 (100).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{38}NO_5Si$: 400.2519; found: 400.2510.

(2*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-5-[(*E*)-2-oxopropylidene]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (7)

A solution of lithium diisopropylamide (0.85 mL, 2 M in heptane, 1.7 mmol) in THF (10 mL) was cooled to –78 °C. Acetone (98 mg, 1.7 mmol) in THF (3 mL) was added over 30 min. After stirring for 30 min at –78 °C, compound **3** (555 mg, 1.7 mmol) in THF (6 mL) was added over 25 min at –78 °C. The solution was allowed to warm to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 50mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (367 mg, 62%) as a pale-yellow oil.

IR (neat): 2928, 2845, 1718, 1578, 1144 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.92 (s, 1 H, C=CH), 4.20–4.13 (m, 1 H, CHN), 3.67 (dd, J = 10.2, 4.9 Hz, 1 H, one of CH$_2$OSi), 3.64 (dd, J = 10.2, 3.4 Hz, 1 H, one of CH$_2$OSi), 3.38 (app ddt, J = 20.1, 9.6, 1.4 Hz, 1 H, one of CH$_2$C=C), 2.95 (dddd, J = 20.1, 11.2, 9.3, 2.2 Hz, 1 H, one of CH$_2$C=C), 2.15 (s, 3 H, CH$_3$CO),

2.02–1.87 (m, 2 H, CH_2), 1.52 [s, 9 H, $(CH_3)_3CO$], 0.82 [s, 9 H, $(CH_3)_3CSi$], 0.00 [s, 3 H, one of $(CH_3)_2Si$], –0.02 [s, 3 H, one of $(CH_3)_2Si$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.5 (ketone C=O), 158.6 (carbamate C=O), 151.5 (*C*=CH), 104.1 (C=*C*H), 82.3 [$(CH_3)_3CO$], 63.8 (CH_2OSi), 62.1 (CHN), 32.0 (CH_3CO), 31.7 (CH_2), 28.3 [$(CH_3)_3CO$], 25.8 [$(CH_3)_3CSi$], 23.9 (CH_2), 21.2 (CSi), –5.2 [one of $(CH_3)_2Si$], –5.5 [one of $(CH_3)_2Si$].

MS-ES: *m*/*z* (%) = 370 (MH^+, 27), 270 (100).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{36}NO_4Si$: 370.2414; found: 370.2403.

(2*S*)-2-(Hydroxymethyl)-5-[(*Z*)-1-ethoxycarbonylmethylidene]pyrrolidine (8)

To a solution of compound **6** (200 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) was added TFA (115 mg, 1.0 mmol) and the solution stirred for 3 h at 25 °C. Sat. aq Na_2CO_3 was added until neutral to pH paper, and the organic material extracted into CH_2Cl_2 (3 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil which was purified by flash column chromatography (eluent: 5:1 hexane–EtOAc) to give the title compound (81 mg, 87%) as a colourless oil.

IR (neat): 3402, 2955, 1714, 1689, 1171 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (br s, 1 H, NH), 4.46 (s, 1 H, C=CH), 4.01 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 3.87 (app quintet, *J* = 5.6 Hz, 1 H, C*H*NH), 3.62 (dd, *J* = 11.2, 3.9 Hz, 1 H, one of CH_2OH), 3.45 (dd, *J* = 11.2, 6.3 Hz, 1 H, one of CH_2OH), 2.53 (m, 2 H, CH_2C=C), 1.99 (m, 1 H, one of CH_2CHN), 1.69 (m, 1 H, one of CH_2CHN), 1.19 (t, *J* = 7.1 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (C=O), 167.3 (C=*C*H), 77.7 (*C*=CH), 65.9 (CH_2O), 61.4 (CH), 59.0 (CH), 32.0 (CH_2CO), 24.0 (CH_2), 14.8 (CH_3).

MS-ES: *m*/*z* (%) = 186 (MH^+, 100).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_9H_{16}NO_3$: 186.1130; found: 186.1125.

(*Z*)-Pyrrolidinylideneacetic Acid Ethyl Ester (9a)

Ethyl 6-*tert*-butoxycarbonylamino-3-oxohexanoate (**4a**; 0.5 g, 1.8 mmol) was dissolved in TFA (0.3 mL, 3.6 mmol) and the resulting solution stirred for 3 h at 25 °C. Sat. aq $NaHCO_3$ was added until neutral to pH paper, and the organic materials extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow solid was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (0.22 g, 78%) as a yellow/orange crystalline solid; mp 62–62.5 °C (Lit.[24] mp 60–62 °C).

IR (CH_2Cl_2): 3360, 2983, 1652, 1590, 1143 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (br s, 1 H, NH), 4.49 (br s, 1 H, alkene CH), 4.05 (q, *J* = 7.1 Hz, 2 H, CH_2O), 3.45 (t, *J* = 6.9 Hz, 2 H, CH_2N), 2.51 (t, *J* = 7.8 Hz, 2 H, CH_2CO), 1.91 (app quintet, *J* = 7.3 Hz, 2 H $CH_2CH_2CH_2$), 1.19 (q, *J* = 7.1 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (C=O), 166.6 (*C*=CH), 76.5 (C=*C*H), 58.4 (CH_2O), 47.1 (CH_2N), 32.2 (CH_2), 22.0 (CH_2), 14.7 (CH_3).

MS-ES: *m*/*z* (%) = 156 (MH^+, 100), 128 (37).

HRMS-ES: *m*/*z* [M + Na]$^+$ calcd for $C_8H_{14}NO_2$ + Na: 156.1025; found: 156.1015.

(*Z*)-Pyrrolidinylideneacetic Acid Benzyl Ester (9b)

Benzyl 6-*tert*-butoxycarbonylamino-3-oxohexanoate (**4b**; 2.0 g, 7.42 mmol) was dissolved in TFA (5.11 g, 44.5 mmol) and stirred for 3 h at 25 °C. Sat. aq $NaHCO_3$ was added until neutral to pH paper, and the organic material extracted into CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (1.5 g, 86%) as a waxy solid; mp 57–58 °C (Lit.[25] mp 75–76 °C).

IR (neat): 3372, 2946, 1651, 1600, 1495, 1454, 1235, 1141, 740, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (br s, 1 H, NH), 5.04 (s, 2 H, CH_2O), 4.54 (br s, 1 H, C=CH), 3.45 (t, *J* = 6.9 Hz, 2 H, CH_2N), 2.52 (t, *J* = 7.8 Hz, 2 H, CH_2CO), 1.90 (app quintet, *J* = 7.3 Hz, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (C=O), 167.0 (*C*=CH), 137.7 (C_{arom}), 128.4 (CH_{arom}), 127.8 (CH_{arom}), 127.6 (CH_{arom}), 76.3 (C=*C*H), 64.4 (CH_2O), 47.1 (CH_2N), 32.3 (CH_2), 22.0 (CH_2).

MS-ES: *m*/*z* (%) = 218 (MH^+, 100), 91 (36).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NO_2$ + Na: 240.1000; found: 240.0995.

(2*Z*)-Pyrrolidinylideneacetic Acid (–)-Menthyl Ester (9c)

(–)-Menthyl 6-*tert*-butoxycarbonylamino-3-oxohexanoate (**4c**; 900 mg, 2.3 mmol) was dissolved in TFA (0.35 mL, 4.6 mmol) and stirred for 3 h at 25 °C. Sat. aq $NaHCO_3$ was added until neutral to pH paper, and the organic material was extracted into CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow solid was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (485 mg, 80%) as a yellow oil.

IR ($CHCl_3$): 3365, 2951, 2868, 1651, 1603, 1236 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H, NH), 4.58 (app dt, *J* = 4.2, 10.8 Hz, 1 H, menthyl 1-H), 4.50–4.35 (br s, 1 H, alkene CH), 3.43 (t, *J* = 6.8 Hz, 2 H, CH_2N), 2.50 (t, *J* = 7.6 Hz, 2 H, CH_2C=C), 1.97–1.82 [m, 4 H, $CH_2CH_2CH_2$ + menthyl 6-H_{eq} + $CH(CH_3)_2$], 1.63–1.55 (m, 2 H, menthyl 3-H_{eq} + 4-H_{eq}), 1.47–1.36 (m, 1 H, menthyl 5-H_{ax}), 1.27 (app br t, *J* = 11.5 Hz, 1 H, menthyl 2-H_{ax}), 0.99 (app dq, *J* = 2.7, 12.7 Hz, 1 H, menthyl 3-H_{ax}), 0.88 (app q, *J* = 11.7 Hz, 1 H, menthyl 6-H_{ax}), 0.87–0.76 (m, 1 H, menthyl 4-H_{ax}), 0.81 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.80 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.70 (d, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5 (C=O), 166.4 (CN), 76.8 (C=*C*H), 71.7 (CHO), 47.3 (CH), 47.1 (CH_2N), 41.6 (CH_2), 34.5 (CH_2), 32.2 (CH_2), 31.5 (CH), 26.3 (CH), 23.7 (CH_2), 22.1 (CH_3), 22.0 (CH_2), 20.8 (CH_3), 16.6 (CH_3).

MS-ES: *m*/*z* (%) = 266 (MH^+, 100), 128 (39).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_2$: 266.2120; found: 266.2139.

(*Z*)-1-Pyrrolidinylidenepropan-2-one (9d)[26]

N-*tert*-Butoxycarbonyl-4,6-dioxoheptylamine (**4d**; 530 mg, 2.2 mmol) was dissolved in TFA (0.34 mL, 4.4 mmol) and stirred for 3 h at 25 °C. Sat. aq $NaHCO_3$ was added until neutral to pH paper, and the organic material extracted into CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow solid was purified by recrystallisation from hexane–Et_2O to give the title compound (233 mg, 85%) as a yellow crystalline solid; mp 52–52.5 °C.

IR ($CHCl_3$): 3272, 1618, 1556, 1505, 1258 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.72 (br s, 1 H, NH), 5.04 (s, 1 H, C=CH), 3.50 (t, *J* = 7.0 Hz, CH_2N), 2.52 (t, *J* = 7.8 Hz, CH_2), 1.96 (s, 3 H, CH_3CO), 1.91 (app quintet, *J* = 7.4 Hz, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0 (C=O), 167.4 (CN), 89.8 (C=*C*H), 47.5 (CH_2N), 32.3 (CH_2), 28.7 (CH_3), 21.4 (CH_2).

MS-ES: *m/z* (%) = 126 (MH^+, 100).

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_7H_{12}NO$: 126.0919; found: 126.0917.

(*Z*)-1-Phenyl-2-pyrrolidinylideneethanone (9e)[26]

To a solution of **4e** (200 mg, 0.65 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.10 mL, 1.3 mmol) and the resulting solution stirred for 3 h at 25 °C. The volatiles were removed in vacuo and the resulting oil dissolved in CH_2Cl_2 (2 mL). Sat. aq Na_2CO_3 was added until neutral to pH paper, and the organic material extracted into CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash column chromatography (eluent: 5:1 hexane–EtOAc) gave the title compound (90 mg, 74%) as a yellow solid; mp 108–109 °C (Lit.[27] mp 108–109 °C).

IR ($CHCl_3$): 3278, 2956, 1700, 1610, 1521, 1260 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.23 (br s, 1 H, NH), 7.80 (dd, *J* = 7.6, 1.9 Hz, CH_{arom}), 7.35–7.29 (m, 3 H, CH_{arom}), 5.70 (s, 1 H, C=CH), 3.56 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$NH), 2.65 (t, *J* = 7.9 Hz, 2 H, C*H*$_2$CCH), 1.95 (app quintet, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.1 (C=O), 169.4 (CN), 140.3 (C_{arom}), 130.5 (CH_{arom}), 128.2 (CH_{arom}), 127.0 (CH_{arom}), 86.6 (C=*C*H), 47.8 (CH_2N), 33.0 (CH_2), 21.4 (CH_2).

MS-ES: *m/z* (%) = 188 (MH^+, 100).

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{12}H_{14}NO$: 188.1075; found: 188.1062.

(2*S*)-5-[(*Z*)-1-Ethoxycarbonylmethylidene]pyrrolidine-2-carboxylic Acid Ethyl Ester (10a)

A solution of **5a** (4.9 g, 14.2 mmol) in TFA (2.1 mL, 28 mmol) was stirred for 3 h at 25 °C. Excess TFA was removed in vacuo and the resulting oil dissolved in CH_2Cl_2 (5 mL). Sat. aq Na_2CO_3 was added until neutral to pH paper, and the organic material extracted into CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (2.6 g, 82%) as a pale-yellow oil.

IR ($CHCl_3$): 3372, 2980, 1738, 1664, 1604, 1196 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (br s, 1 H, NH), 4.53 (br s, 1 H, C=CH), 4.29 (dd, *J* = 8.3, 5.2 Hz, CHN), 4.16–4.11 (m, 2 H, CH_2O), 4.03 (q, *J* = 7.1 Hz, CH_2O), 2.63 (ddd, *J* = 16.7, 8.1, 7.0 Hz, 1 H, one of CH_2C=C), 2.57–2.50 (m, 1 H, one of CH_2C=C), 2.23 (app ddt, *J* = 12.9, 7.1, 8.6 Hz, 1 H, one of CH_2), 2.05 (app ddt, *J* = 12.9, 9.0, 5.6 Hz, 1 H, one of CH_2), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.19 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C=O), 170.4 (C=O), 164.9 (CN), 78.8 (C=*C*H), 61.5 (OCH_2), 60.5 (CHN), 58.7 (OCH_2), 31.1 (CH_2), 26.2 (CH_2), 14.6 (CH_3), 14.2 (CH_3).

MS-ES: *m/z* (%) = 250 (M + Na, 34), 228 (MH^+, 100), 182 (13).

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{11}H_{18}NO_2$: 228.1236; found: 228.1239.

(2*S*)-5-[(*Z*)-1-(–)-Benzyloxycarbonylmethylidene]pyrrolidine-2-carboxylic Acid Ethyl Ester (10b)

A solution of **5b** (2.45 g, 6.01 mmol) in TFA (4.11 g, 36 mmol) was stirred for 3 h at 25 °C. Sat. aq $NaHCO_3$ was added until neutral to pH paper, and the organic material extracted into CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (1.26 g, 72%) as a yellow oil.

IR (neat): 3366, 2979, 2905, 1738, 1665, 1602, 1454, 1373, 1198, 1144, 1023, 739, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (br s, 1 H, NH), 7.32–7.16 (m, 5 H_{arom}), 5.07 and 5.02 (AB quartet, *J* = 12.6 Hz, 2 H, PhC*H*$_2$O), 4.28 (dd, *J* = 8.3, 5.2 Hz, CHN), 4.16–4.09 (m, 2 H, CH_2O), 2.68–2.45 (m, 2 H, CH_2C=C), 2.28–2.16 (m, 1 H, one of CH_2), 2.10–1.97 (m, 1 H, one of CH_2), 1.21 (3 H, t, *J* = 7.1 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (C=O), 170.0 (C=O), 165.4 (*C*=CH), 135.2 (C_{arom}), 128.5 (CH_{arom}), 127.9 (CH_{arom}), 127.7 (CH_{arom}), 78.5 (C=*C*H), 64.6 (O*C*H$_2$Ph), 61.5 (OCH_2), 60.5 (CHN), 31.2 (CH_2), 26.1 (CH_2), 14.2 (CH_3).

MS-ES: *m/z* = 290 (MH^+, 100%).

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{16}H_{20}NO_4$: 290.1392; found: 290.1382.

(2*S*)-5-[(*Z*)-1-(–)-Menthyloxycarbonylmethylidene]pyrrolidine-2-carboxylic Acid Ethyl Ester (10c)

TFA (0.23 mL, 3 mmol) was added to a solution of **5c** (696 mg, 1.53 mmol) in CH_2Cl_2 (10 mL). After stirring for 3 h at 25 °C, the solution was neutralized with sat. aq Na_2CO_3 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 10:1 CH_2Cl_2–MeOH) to give the title compound (387 mg, 75%) as a white crystalline solid; mp 72.0–72.5 °C.

IR (Nujol): 3370, 1738, 1661, 1605, 1200 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (br s, 1 H, NH), 4.58 (app dt, *J* = 4.3, 10.8 Hz, 1 H, menthyl 1-H$_{ax}$), 4.52 (s, 1 H, C=*C*H), 4.28 (dd, *J* = 8.3, 5.4 Hz, 1 H, CHN), 4.17–4.09 (m, 2 H, OCH_2), 2.63 (dddd, *J* = 16.6, 8.9, 6.8, 0.7 Hz, 1 H, one of CH_2CO), 2.52 (dddd, *J* = 16.6, 8.9, 6.3, 0.7 Hz, 1 H, one of CH_2CO), 2.22 (app ddt, *J* = 12.8, 6.9, 8.6 Hz, 1 H, one of C*H*$_2$CH$_2$CO), 2.09–2.01 (m, 1 H, one of C*H*$_2$CH$_2$CO), 1.98–1.92 (m, 1 H, menthyl 6-H$_{eq}$), 1.87 [app doubled septet, *J* = 2.6, 7.0 Hz, 1 H, C*H*(CH$_3$)$_2$], 1.63–1.56 (m, 2 H, menthyl 3-H$_{eq}$ + 4-H$_{eq}$), 1.47–1.39 (m, 1 H, menthyl 5-H$_{ax}$), 1.32–1.25 (m, 1 H, menthyl 2-H$_{ax}$), 1.21 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$), 1.00 (app dq, *J* = 3.5, 13.0 Hz, 1 H, menthyl 3-H$_{ax}$), 0.89 (app q, *J* = 11.7 Hz, 1 H, menthyl 6-H$_{ax}$), 0.82 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.81 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.80–0.75 (m, 1 H, menthyl 4-H$_{ax}$), 0.70 (d, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (ester C=O), 170.0 (ester C=O), 164.7 (*C*=CH), 79.2 (C=*C*H), 72.1 (menthyl 1-CH), 61.5 (CH_2O), 60.4 (CHN), 47.2 (menthyl 2-CH), 41.5 (menthyl 6-CH_2), 34.4 (menthyl 4-CH_2), 31.4 (menthyl 5-CH), 31.1 (*C*H$_2$C=C), 26.2 [*C*H(CH$_3$)$_2$], 26.1 (CH$_2$*C*H$_2$CHN), 23.6 (menthyl 3-CH_2), 22.1 (CH_3), 20.8 (CH_3), 16.5 (CH_3), 14.2 (CH_3).

MS-ES: *m/z* (%) = 360 ([M + Na]$^+$, 12), 339 (22), 338 (100).

HRMS-ES: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{31}NO_4$ + Na: 360.2151; found: 360.2155.

(2*S*)-5-[(*Z*)-2-Oxopropylidene]pyrrolidine-2-carboxylic Acid Ethyl Ester (10d) [28]

A solution of **5d** (400 mg, 1.27 mmol) in CH_2Cl_2 (3 mL) and TFA (0.16 mL, 2.4 mmol) was stirred for 3 h at 25 °C. After removal of the volatiles in vacuo, the resulting oil was dissolved in CH_2Cl_2 (5 mL). Sat. aq Na_2CO_3 was added until neutral to pH paper and the organic material was extracted into CH_2Cl_2 (3 × 50 mL). The combined organic layers dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (138 mg, 55%) as a pale-yellow oil.

IR (neat): 3297, 2982, 1740, 1628, 1555, 1202 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.80 (br s, 1 H, NH) 5.10 (br s, 1 H, C=CH), 4.35 (dd, *J* = 8.5, 5.1 Hz, CHN), 4.18–4.10 (m, 2 H, OCH_2), 2.65 (ddd, *J* = 16.9, 8.9, 7.3 Hz, one of CH_2C=C), 2.54 (ddd, *J* = 16.9, 9.1, 5.9 Hz, one of CH_2C=C), 2.27–2.19 (m, 1 H, one of CH_2), 2.10–2.02 (m, 1 H, one of CH_2), 1.98 (s, 3 H, CH_3), 1.22 (t, *J* = 7.1 Hz, C$H_3$$CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.0 (ketone C=O), 171.6 (ester C=O), 165.8 (*C*=CH), 91.0 (C=*C*H), 61.6 (OCH_2), 61.0 (CH), 31.3 (CH_2), 28.9 (CH_3), 25.6 (CH_2) and 14.1 (CH_3).

MS-ES: *m*/*z* = 198 (MH^+, 100%).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}NO_3$: 198.1130; found: 198.1131.

(2*S*)-5-[(*Z*)-2-Oxo-2-phenylethylidene]pyrrolidine-2-carboxylic Acid Ethyl Ester (10e)

A solution of **5e** (377 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) and TFA (0.13 mL, 2 mmol) was stirred for 3 h at 25 °C. After removal of the volatiles in vacuo, the resulting oil was dissolved in CH_2Cl_2 (5 mL) and sat. aq Na_2CO_3 was added until neutral to pH paper. The organic material was extracted into CH_2Cl_2 (3 × 50 mL), the combined organic layers dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash column chromatography (eluent: 7:1 hexane–EtOAc) to give the title compound (114 mg, 44%) as a pale-yellow crystalline solid; mp 64–64.5 °C.

IR ($CHCl_3$): 3288, 2981, 1740 (v br), 1615, 1522, 1210 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.32 (br s, 1 H, NH), 7.87–7.84 (m, 2 H_{arom}), 7.42–7.35 (m, 3 H_{arom}), 5.84 (s, 1 H, C=CH), 4.47 (dd, *J* = 8.6, 5.4 Hz, 1 H, CHN), 4.24–4.16 (m, 2 H, OCH_2), 2.84 (ddd, *J* = 17.1, 9.1, 7.0 Hz, 1 H, one of CH_2C=C), 2.73 (ddd, *J* = 17.1, 8.9, 5.8 Hz, 1 H, one of CH_2C=C), 2.34 (dddd, *J* = 13.0, 8.9, 8.6, 7.0 Hz, 1 H, one of CH_2), 2.18 (dddd, *J* = 13.0, 9.1, 5.8, 5.4 Hz, 1 H, one of CH_2), 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8 (ketone C=O), 171.4 (ester C=O), 167.7 (*C*=CH), 139.9 (C_{arom}), 130.8 (CH_{arom}), 128.2 (CH_{arom}), 127.2 (CH_{arom}), 87.5 (C=*C*H), 61.7 (OCH_2), 61.3 (CH), 31.9 (CH_2), 25.6 (CH_2), 14.2 (CH_3).

MS-ES: *m*/*z* = 260 (MH^+, 100%).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1271.

***N*-*tert*-Butoxycarbonyl-4-oxo-5-phenylsulfonylpentylamine (11)[14]**

A solution of *n*-BuLi (2 mL, 2.5 M in hexanes, 5 mmol) in THF (10 mL) was cooled to –78 °C. Methyl phenyl sulfone (0.77 g, 5 mmol) in THF (3 mL) was added over 30 min, after which the solution was stirred for a further 30 min at –78 °C. *N*-*tert*-Butoxycarbonylpyrrolidin-2-one (**1**; 0.92 g, 5 mmol) in THF (5 mL) was added over 30 min at –78 °C, and the solution warmed to 25 °C and left to stir for 18 h. Sat. aq NH_4Cl (100 mL) was added and the solution extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give the title compound (1.8 g, 96%) as an orange oil which solidified upon standing to give a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.4 Hz, 2 H_{arom}), 7.62 (t, *J* = 7.5 Hz, 1 H_{arom}), 7.52 (app t, *J* = 7.7 Hz, 1 H_{arom}), 4.62 (br s, 1 H, NH), 4.15 (s, 2 H, OCCH_2CO), 3.03 (app q, *J* = 6.4 Hz, 2 H, CH_2NH), 2.70 (t, *J* = 6.8 Hz, 2 H, $COCH_2$), 1.69 (app quintet, *J* = 6.8 Hz, CH_2C$H_2$$CH_2$), 1.36 [s, 9 H, C(C$H_3$)$_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8 (CH_2*C*OCH_2), 156.1 (OCON), 138.7 (C_{arom}), 134.4 (CH_{arom}), 129.4 (CH_{arom}), 128.3 (CH_{arom}), 79.3 (O*C*CMe$_3$), 67.0 (CH_2O), 41.4 (CH_2N), 39.3 (COCH_2CO), 28.4 [C(*C*H$_3$)$_3$], 23.7 (*C*$H_2$$CH_2$N).

(*Z*)-2-Phenylsulfonylmethylylidenepyrrolidine (12)[14]

To a solution of **11** (1.4 g, 4.1 mmol) in CH_2Cl_2 (5 mL) was added TFA (3.48 mL, 45 mmol) and the solution stirred for 18 h at 25 °C. The volatiles were removed in vacuo and the resulting oil was dissolved in CH_2Cl_2 (5 mL). Sat. aq $NaHCO_3$ was added until neutral to pH paper, and the organic material was extracted into CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The residual yellow oil was purified by flash column chromatography (eluent: 4:1 hexane–EtOAc) to give the title compound (620 mg, 67%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 6.7 Hz, 2 H_{arom}), 7.43–7.34 (m, 3 H_{arom}), 7.05 (br s, 1 H, NH), 4.58 (s, 1 H, CCH), 3.38 (t, *J* = 6.9 Hz, 2 H, CH_2N), 2.48 (t, *J* = 7.8 Hz, 2 H, CH_2CO), 1.86 (app quintet, *J* = 7.3 Hz, 2 H, CH_2C*H*$_2$$CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9 (*C*=CH), 145.4 (C_{arom}), 131.8 (CH_{arom}), 128.1 (CH_{arom}), 125.6 (CH_{arom}), 80.8 (C=*C*H), 47.5 (CH_2N), 33.2 (CH_2C=C), 21.7 (*C*$H_2$$CH_2$N).

Acknowledgment

We thank the EPSRC for a studentship (S.V.W.) and to Mr. R. L. Jenkins for technical assistance. We are grateful to Mr. J. L. Wood for the preparation of compounds **5b** and **9b**.

References

(1) For a review, see: Elliott, M. C.; Wood, J. L.; Wordingham, S. V. *Trends Heterocycl. Chem.* **2006**, in press.
(2) Shiosaki, K. *Compr. Org. Synth.* **1991**, *2*, 865.
(3) Célérier, J.-P.; Deloisy, E.; Lhommet, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089.
(4) (a) Elliott, M. C.; Long, M. S. *Tetrahedron Lett.* **2002**, *43*, 9191. (b) Elliott, M. C.; Long, M. S. *Org. Biomol. Chem.* **2004**, *2*, 2003.
(5) (a) Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3519. (b) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227.
(6) (a) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329. (b) Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; García Navio, J. L.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **1993**, *34*, 6317. (c) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669. (d) v. Keyserlingk, N. G.; Martens, J. *Eur. J. Org. Chem.* **2002**, 301. (e) Mori, M.; Tomita, T.; Kita, Y.; Kitamura, T. *Tetrahedron Lett.* **2004**, *45*, 4397. (f) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895. (g) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301. (h) Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 5921.
(7) (a) Coutts, I. G. C.; Saint, R. E. *Tetrahedron Lett.* **1998**, *39*, 3243. (b) Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* **2000**, *41*, 7299.
(8) (a) Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwé, D. *Tetrahedron* **1998**, *54*, 1753. (b) Momotake, A.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (c) Yokoyama, M.; Ikenogami, T.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2067.
(9) (a) Molina, M. T.; del Valle, C.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1993**, *49*, 3801. (b) de Blas, J.; Dominguez, E.; Ezquerra, J. *Tetrahedron Lett.* **2000**, *41*, 4567.
(10) Ohta, T.; Kimura, T.; Sato, N.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 4303.
(11) Ezquerra, J.; de Mendoza, J.; Pedregal, C.; Ramírez, C. *Tetrahedron Lett.* **1992**, *33*, 5589.

(12) (a) Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J. H.; García Ruano, J. L. *Tetrahedron Lett.* **1993**, *34*, 4989. (b) Mota, A. J.; Langlois, N. *Tetrahedron Lett.* **2003**, *44*, 1141. (c) Mota, A. J.; Chiaroni, A.; Langlois, N. *Eur. J. Org. Chem.* **2003**, 4187.
(13) (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163. (b) Langlois, N. *Org. Lett.* **2002**, *4*, 185.
(14) Arias, L. A.; Arbelo, D.; Alzérreca, A.; Prieto, J. A. *J. Heterocycl. Chem.* **2001**, *38*, 29.
(15) For formation of alkylidenepyrrolidines from ε-amino-β-keto esters prepared by other methods, see: (a) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Org. Chem.* **1985**, *50*, 5352. (b) Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668. (c) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515. (d) Michael, J. P.; Hosken, G. D.; Howard, A. S. *Tetrahedron* **1988**, *44*, 3025. (e) Calvet, S.; David, O.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron* **2003**, *59*, 6333. (f) Wang, M.-X.; Liu, Y.; Gao, H.-Y.; Zhang, Y.; Yu, C.-Y.; Huang, Z. T.; Fleet, G. W. J. *J. Org. Chem.* **2003**, *68*, 3281.
(16) Pichon, M.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1996**, *37*, 7963.
(17) Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett.* **2003**, *5*, 1847.
(18) Ikota, N. *Chem. Pharm. Bull.* **1992**, *40*, 1925.
(19) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(20) Célérier, J.-P.; Deloisy-Marchalant, E.; Lhommet, G. *J. Heterocycl. Chem.* **1984**, *21*, 1633.
(21) A *Chemical Abstracts* search of compound **9a** reveals 21 references to the *Z*-isomer and 6 to the *E*-isomer. However, the reports of the *E*-isomer only mention this compound in passing, and to the best of our knowledge full characterisation data has never been reported for this double-bond isomer. We are unaware of examples where full characterisation data of both the *E*- and *Z*-isomers of a single alkylidenepyrrolidine have been reported.
(22) Bachi, M. D.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439.
(23) The free alcohol corresponding to this compound is known: Hussaini, S. R.; Moloney, M. G. *Org. Biomol. Chem.* **2003**, 1838.
(24) Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Eur. J. Org. Chem.* **2005**, 505.
(25) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Tetrahedron* **1995**, *51*, 8613.
(26) Delbecq, P.; Celerier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1990**, *31*, 4873.
(27) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron Lett.* **1996**, *37*, 7749.
(28) Honda, T.; Kimura, M. *Org. Lett.* **2000**, *2*, 3925.