Efficient tin hydride-mediated radical cyclisation of secondary amides. Part 1. Synthesis of a variety of substituted pyrrolidinones

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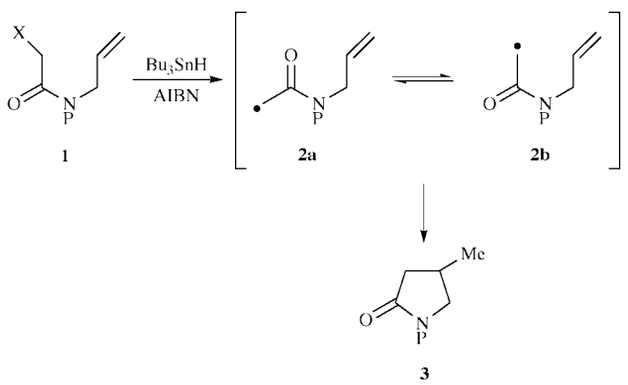
The tin hydride-mediated 5-*exo-trig* cyclisation of a variety of secondary haloamides under mild, neutral reaction conditions has been investigated. Cyclisation was found to produce substituted pyrrolidinones in good to reasonable yield when the reaction was carried out in boiling toluene; lower yields were observed when using boiling benzene. The predominant formation of the *trans*-(C-3–C-4) isomers is consistent with a reversible cyclisation leading to the thermodynamically more stable product. The nature of the acceptor carbon–carbon double bond and substituents at the radical centre were found to influence the stereoselectivity of the cyclisation: more of the *cis*-isomer was isolated from precursors bearing a radical stabilising group on the alkene. This can be explained by a slower radical ring opening (or fragmentation) reaction leading to more of the kinetic (*cis*) product. The introduction of substituents alpha to nitrogen (which can influence the amide conformer population) improved the yield of cyclisation and substituted pyrrolidinones could be isolated in up to 76% yield.

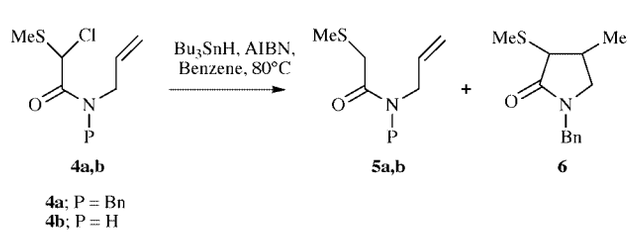
Introduction

One important method for preparing substituted pyrrolidinones **3** involves free-radical cyclisation of unsaturated haloamide precursors **1** using tributyltin hydride (Scheme 1).[1]



Scheme 1

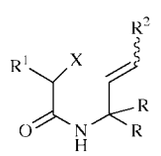
These reactions, which proceed *via* a 5-*exo-trig* pathway, employ neutral conditions and the yields of cyclisation are often excellent when a nitrogen protecting group (*e.g.* P = $COCF_3$, Ph or Bn *etc*.) is utilised. For example, reaction of the *N*-benzyl amide **4a** with tin hydride (in boiling benzene) yielded the pyrrolidinone **6** in 80% yield and 12% of the acyclic amide **5a** while reaction of the corresponding secondary amide **4b** only gave the product of simple reduction, **5b**, in 36% yield (Scheme 2).[2] The importance of a large bulky protecting group



Scheme 2

on nitrogen has been explained in terms of the conformer population of the intermediate carbamoylmethyl radical **2** (Scheme 1).[2,3] A large *N*-protecting group favours the *anti*-conformer **2b** (over the *syn*-conformer **2a**) which can cyclise on to the alkene double bond. The rate constant for this type of cyclisation (on to a terminal alkene) has recently been estimated to be in the range $0.5–1.0 \times 10^6$ s^{-1} at ambient temperature.[4] At 20 °C, the rate of rotation of the N–CO bond in **2a** is approximately ten times slower than the rate of reaction with tributyltin hydride leading to the product of simple reduction.[4] Hence the need to carry out cyclisations at elevated temperatures using a low concentration (*i.e.* slow addition) of tin hydride.

We became interested in developing an efficient cyclisation of secondary haloamides **7** and envisaged that the amide con-



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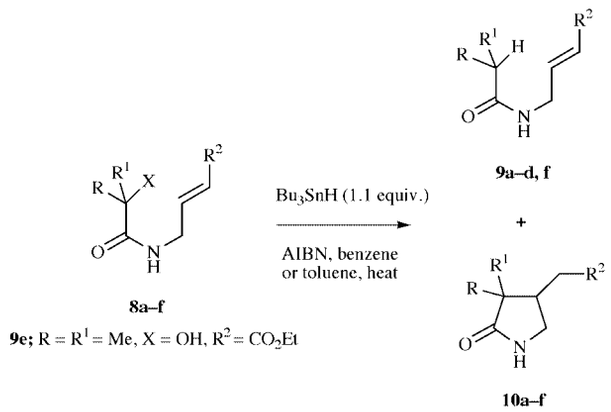
former population and/or the rate of 5-*exo-trig* radical cyclisation would be influenced by substitution at positions other than nitrogen. Substitution at three additional sites was thought to be important and worthy of investigation: (i) at the α-carbon (R) which could alter the conformer population because of steric interactions with the amide side chain; (ii) at the site of radical generation (R^1) as this would influence the lifetime and philicity of the carbamoylmethyl radical as well as the conformer population and (iii) at the acceptor double bond (R^2) leading to different rates of cyclisation on to electron rich or poor double bonds. The cyclisation of a number of haloamides with various substituents at these three positions, to give substituted pyrrolidinones, is now reported.[5]

Results and discussion

Initial work explored the reaction of tributyltin hydride (added over 1 h) with haloethanamides **8a–f** in boiling benzene or

Table 1 Tin hydride mediated cyclisations of **8a–f**

Entry	**8**	R	R^1	R^2	X	*T*/°C	**9** (%)	**10** (%)	**10** *trans*:*cis*
1	**a**	Cl	Cl	H	Cl	80	56	16	—
2	**a**	Cl	Cl	H	Cl	110	18	30	—
3	**b**	Cl	Cl	CO_2Et	Cl	110	13	61	—
4	**c**	Ph	H	H	Cl	110	29	45	8.5:1
5	**d**	Ph	H	CO_2Et	Cl	110	20	42	3.1:1
6	**e**	Me	Me	CO_2Et	Br	110	21	30	—
7	**f**	Cl	H	CO_2Et	Cl	110	24	53	1.4:1



Scheme 3

toluene (Scheme 3, Table 1). The cyclisation precursors **8a–f** were prepared from allylamine using standard acylation, oxidative alkene cleavage (OsO_4, $NaIO_4$) and Wittig procedures.[6] Reaction of **8a** at 80 °C gave the acyclic amide **9a**, derived from simple reduction, as the major product. Cyclisation to give **10a** was only observed in 16% yield. This yield could be improved to 30% when the same reaction was carried out at 110 °C in boiling toluene. The higher temperature was expected to increase the rate of rotation around the N–CO bond leading to a higher proportion of the *anti*-carbamoylmethyl radical (of type **2b**) which can cyclise. Reaction of α,β-unsaturated ester **8b**, under the same conditions, was found to give a higher yield of cyclised product (61%). The carbamoylmethyl radical intermediate (with an amide and two chloro substituents) is expected to be electrophilic in nature. As a result, cyclisation on to the electron poor double bond present in **8b** would be expected to be slower than cyclisation on to an electron rich terminal alkene (as in **8a**); this is because of a less favourable (SOMO–HOMO) orbital interaction. The higher yield of **8b** over **8a** is therefore surprising. However, these cyclisations are believed to be reversible (see later) and the stability of the cyclised radical could be a decisive factor. Cyclisation to **10b** proceeds *via* a secondary pyrrolidinone radical, which is stabilised by the ester substituent, while the formation of **10a** involves the intermediacy of a less stable primary radical. This rationale does not, however, account for the reaction of benzylic chlorides **8c–d** where similar yields of cyclisation to give **10c** and **10d**, respectively, were observed. Precursors **8e–f** with alternative substitution (at the site of radical generation) were also found to undergo cyclisation to give pyrrolidinones in 30 and 53% yield, respectively. Cyclisation of **8e** was accompanied by the isolation of alcohol **9e** (derived from hydrolysis of **8e**) and other inseparable by-products (typically <20%). The stereochemistry of the (inseparable) pyrrolidinone diastereomers **10c**, **10d** and **10f**, was assigned on the basis of γ-*gauche* effects in the ^{13}C NMR spectra. For **10c**, for example, the methyl carbon in the *cis*-isomer is more shielded (δ 15.0 ppm) than in the *trans*-isomer (δ 17.3 ppm). The chemical shift of the PhCH hydrogen in **10c** and **10d** is also indicative; the shift of the PhCH hydrogen in the *cis*-diastereomer being appreciably higher (*e.g.* δ 3.64 ppm) than that for the *trans* (*e.g.* δ 3.08 ppm). This is consistent with previously reported trends in similar systems.[7,8]

The pyrrolidinone diastereoselectivity was influenced by the nature of the substituents at the site of radical generation and on the alkene double bond. The phenyl derivative **8c** gave predominantly the *trans*-diastereomer **10c**, consistent with a reversible cyclisation (Scheme 4), leading to the thermodynamically

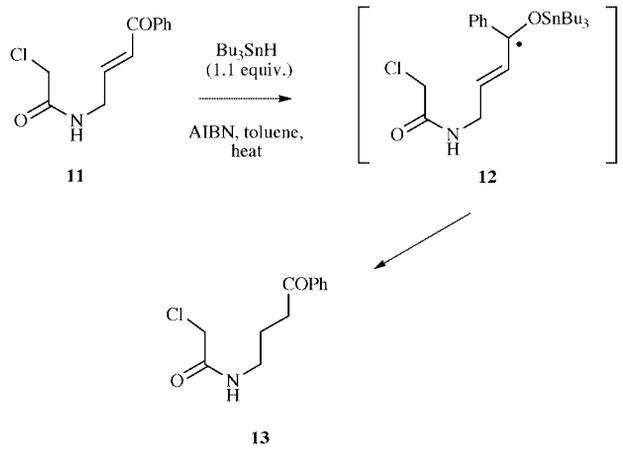
Scheme 4

more stable product. This is in line with results published by Walling and Cioffari[9] on the related (carbocyclic) 1-phenylhex-5-enyl system; tin-mediated cyclisation gave exclusively the *trans*-disubstituted cyclopentane. Both radical cyclisations are reversible because of the stability of the first-formed benzylic radicals which lead to a competitive ring opening process (estimated to be 1×10^5 s^{-1} for the 1-methyl-2-phenylcyclopentenyl radical[9] at 70 °C). Cyclisation of carbamoylmethyl radicals, with various α-substituents, have also been shown[8] to give significant amounts of the *trans*-pyrrolidinone isomer; this can be related to radical stabilisation by the amide carbonyl group. Introduction of an ester substituent on the acceptor double bond in **8d** was shown to lower the pyrrolidinone diastereoselectivity. The ester substituent is expected to stabilise the cyclised radical leading to a slower rate of ring opening and hence a greater proportion of the *cis*-pyrrolidinone isomer. When the phenyl group is replaced by a chloro substituent, as in **8f**, the cyclisation affords almost equal amounts of the *cis*- and *trans*-isomers of **10f**. This can be explained by the relative stability of the initial carbamoylmethyl radicals; the α-chloro substituent is not expected to stabilise the radical as effectively as the phenyl substituent leading to a slower rate of ring opening and reformation of the carbamoylmethyl radical.†

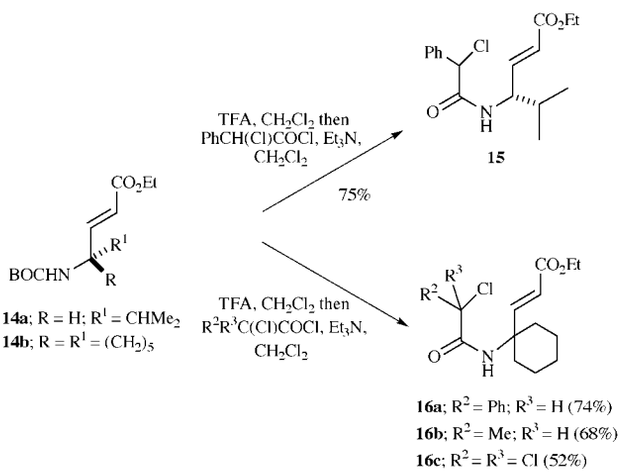
Attempted cyclisation of a secondary haloamide bearing an unsaturated ketone (rather than ester) side chain was unsuccessful. Treatment of ketone **11** with tributyltin hydride (1.1 equivalents) surprisingly resulted in the chemoselective reduction of the alkene double bond to give butanone **13** in 40% yield (Scheme 5). This was thought to be derived from addition of the tin radical to the ketone (rather than abstraction of the chlorine atom) to give allylic *O*-stannyl ketyl radical **12**. Subsequent reaction with tin hydride and hydrolysis (on workup) led to the reduced product **13**.[12]

Encouraged by the radical cyclisation of unsaturated esters, we then explored the effect of substitution at the carbon atom α to nitrogen. Bulky alkyl substituents were introduced at this position as these could influence the amide conformer population and improve the efficiency of the cyclisation reaction. The isopropyl substituted alkene **14a** was prepared in four steps

† The greater stability of the benzylic radical is reflected in the lower C–H bond dissociation energy for toluene ($PhCH_2$–H, 368 kJ mol^{-1})[10] *versus* chloromethane ($ClCH_2$–H, 422 kJ mol^{-1}).[11]



Scheme 5



Scheme 6

from (*S*)-valine as described previously (Scheme 6).[13] The key step involved a Wittig reaction of an intermediate *N*-Boc α-amino aldehyde[14] and a similar approach was used to prepare the cyclohexyl derivative **14b** from 1-aminocyclohexane-1-carboxylic acid. These carbamates were deprotected to give the primary amines that were then acylated to afford chloroamides **15** and **16a–c** in good yield.

Reaction of the isopropyl precursor **15** with tin hydride in boiling toluene produced the trisubstituted pyrrolidinones **17–19** in a combined 56% yield (Scheme 7, Table 2). Only 4% of the simple reduced product **20** was isolated and so introduction of the isopropyl group increased the efficiency of the radical cyclisation by 14% (*cf.* cyclisation of **8d** to give **10d** in 42% yield).‡ The predominant formation of the all *trans*-pyrrolidinone **17** is consistent with a reversible cyclisation reaction and the C-3–C-4 *trans*:*cis* ratio (4.5:1) is akin to that observed for **10d** (3.1:1).§ A very similar result was obtained from reaction of a related (*S*)-leucine derived precursor with an isobutyl rather than isopropyl side chain. This gave the trisubstituted pyrrolidinone in 58% yield (as an 8.4:2.2:1 mixture of diastereoisomers) together with the product of simple reduction in 4% yield. Once again, the major pyrrolidinone diastereoisomer possessed the all-*trans* configuration.

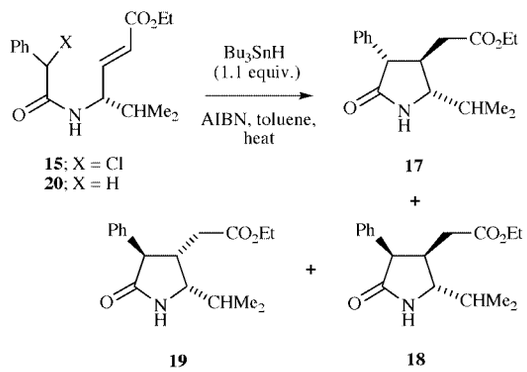
Cyclisation of the cyclohexyl precursor **16a** was found to be even more efficient and pyrrolidinones **21a** and **22a** were

‡ Substituted propargyl bromoamides have been shown to undergo efficient radical cyclisation.[15]

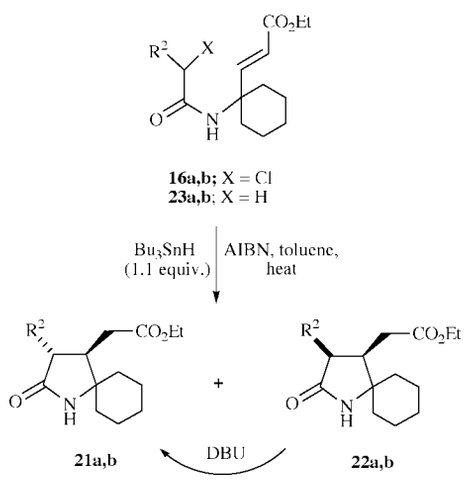
§ The stereochemistry of **17–19** was determined from a comparison of the ^{1}H and ^{13}C NMR spectra of related trisubstituted pyrrolidinones that are reported in the following paper.

Table 2 Tin hydride mediated cyclisations of **15** and **16a–c**

Entry	Chloride	Products (yield %)
1	**15**	**17** (36) + **18** (16) + **19** (4) + **20** (4)
2	**16a**	**21a** (54) + **22a** (14) + **23a** (3)
3	**16b**	**21b** (51) + **22b** (25) + **23b** (4)
4	**16c**	**24** (58)

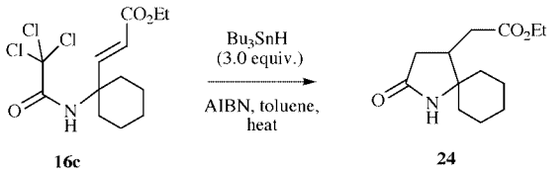


Scheme 7



Scheme 8

formed in a combined 68% yield (or 73% based on recovered **16a**) (Scheme 8, Table 2). The cyclohexane ring effectively restricts the conformation of the chain to increase the population of the *anti*-amide conformer (of type **2b**). As for the earlier cyclisations, the *trans*-C-3–C-4 isomer **21a** was formed predominantly in a reversible cyclisation reaction. The stereochemistry of the spirocyclic products was determined from the ^{13}C NMR spectra and confirmed by epimerisation at C-3 using DBU in boiling toluene; this cleanly converted the *cis*-isomer **22a** to the thermodynamically more stable *trans*-isomer **21a**. Related cyclohexyl precursors, with different substituents at the radical centre, were also found to undergo efficient cyclisation (Scheme 8 and 9, Table 2). Hence the methyl derivative **16b** underwent cyclisation in an excellent 76% yield while reaction of trichloroamide **16c** with 3.0 equivalents of tin hydride gave **24** in 58% yield (or 78% based on recovered starting material). The cyclisation of **16b** was less diastereoselective than for **16a** (*i.e.* 2:1 *versus* 3.9:1) presumably because the phenyl substituent stabilises the carbamoyl radical more effectively than the methyl substituent. This leads to a faster rate of ring opening and equilibration gives more of the *trans*-pyrrolidinone isomer.



16c 24

Scheme 9

This work has demonstrated that secondary haloamides, without bulky *N*-protecting groups, can undergo efficient free-radical cyclisation in boiling toluene. Reaction of a variety of substituted precursors has shown that the position and nature of the substitution has an effect on both the efficiency and diastereoselectivity of the cyclisation reaction. These cyclisations allow the formation of substituted pyrrolidinones of considerable synthetic interest.

Experimental

IR spectra were recorded on an ATI Mattson Genesis FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 270, Varian Unity+ or a Bruker AMX500 spectrometer. The spectra were assigned using DEPT experiments. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5 Hz. Only those peaks visible and clearly attributable are reported for minor diastereoisomers. Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec Spectrometer system. Optical rotations were recorded at ambient temperature on a Jasco DIP-370 polarimeter. Concentration (*c*) is expressed in g per 100 cm^3. Thin layer chromatography (TLC) was performed on Merck aluminium-backed silica gel plates. Compounds were visualised under a UV lamp, using basic potassium permanganate solution, acidic cerium(IV) sulfate–molybdic acid solution and/or iodine. Column chromatography was perfomed using silica gel (Matrex Silica 60, 70–200 micron Fisons or ICN flash silica 60, 32–63 micron). Solvents were purified/dried using standard literature methods. Petroleum ether refers to the fraction with bp 40–60 °C. Bu_3SnH was purchased from Lancaster Synthesis Ltd and distilled immediately before use.

General procedure for radical cyclisation

To a stirred solution of the halide **8a**–**f** (1.0 equiv., 0.15–0.74 mmol) in boiling degassed toluene (7–30 cm^3) under nitrogen was added, *via* a syringe pump over 1 h, a solution containing tributyltin hydride (1.1 equiv., 0.18–0.81 mmol) and azobisisobutyronitrile (0.03–0.15 mmol) in toluene (14–60 cm^3) and the reaction heated at reflux for 6–18 h. The solvent was removed *in vacuo* and equal volumes of 8% aqueous potassium fluoride and diethyl ether were added to the residue before stirring vigorously for 1 h. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford crude product. Column chromatography (silica) afforded the pyrrolidines **10a**–**f** (16–61%) and acyclic amides **9a**–**f** (13–56%) as oils.

(Dichloroethanamido)propene 9a. R_f 0.6 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3429 (s), 3087 (w), 2929 (w), 1690 (s), 1531 (s), 1424 (w), 1266 (m), 989 (m), 811 (m), 724 (w); δ_H (270 MHz, $CDCl_3$) 6.67 (1H, br s, NH), 5.96 (1H, s, C*H*Cl$_2$), 5.87 (1H, ddt, *J* = 17, 10, 4.5, CH=CH$_2$), 5.28 (1H, ddt, *J* = 17, 3, 1.5, CH=C*H*$_A$H$_B$), 5.21 (1H, ddt, *J* = 10.5, 3, 1.5, CH=CH$_A$*H*$_B$), 3.97 (2H, dt, *J* = 6, 1.5, NHC*H*$_2$); δ_C (67.5 MHz, $CDCl_3$) 164.3 (*C*ONH), 132.5 (*C*H=CH$_2$), 117.1 (CH=*C*H$_2$), 66.3 (*C*HCl$_2$), 42.4 (NH*C*H$_2$); *m*/*z* (CI, NH_3) 189 (^{37,37}M + NH_4^+, 13%), 187 (^{37,35}M + NH_4^+, 64), 185 (^{35,35}M + NH_4^+, 100), 153 (6), 151 (13), 134 (4), 132 (12), 115 (10), 56 (6) (Found: ^{35,35}M + NH_4^+, 185.0248. $C_5H_7Cl_2NO$ requires for ^{35,35}M + NH_4^+, 185.0248).

3,3-Dichloro-4-methylpyrrolidin-2-one 10a. R_f 0.4 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3433 (w), 1742 (m), 1224 (w), 755 (s); δ_H (270 MHz, $CDCl_3$) 7.77 (1H, br s, N*H*), 3.46 (1H, dd, *J* = 9, 7, NHC*H*$_A$H$_B$), 3.08 (1H, dd, *J* = 10, 9, NHCH$_A$*H*$_B$), 2.88 (1H, app. sextet, *J* = 6, C*H*CH$_3$), 1.31 (3H, d, *J* = 7, CHC*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 170.4 (*C*ONH), 86.6 (Cl$_2$*C*), 47.3 (*C*HCH$_3$), 45.7 (NH*C*H$_2$), 11.7 (CH*C*H$_3$); *m*/*z* (CI, NH_3) 189 (^{37,37}M + NH_4^+, 11%), 187 (^{37,35}M + NH_4^+, 64), 185 (^{35,35}M + NH_4^+, 100), 172 (^{37,37}M + H^+, 10), 170 (^{37,35}M + H^+, 64), 168 (^{35,35}M + H^+, 99), 153 (6), 151 (18), 136 (15), 134 (51), 118 (6), 109 (6), 98 (13), 89 (16) (Found: ^{35,35}M + H^+, 167.9980. $C_5H_7Cl_2NO$ requires for ^{35,35}M + H^+, 167.9983).

Ethyl (*E*)-4-(2,2-dichloroethanamido)but-2-enoate 9b. R_f 0.4 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3430 (m), 3005 (w), 1705 (s), 1664 (m), 1525 (m), 1308 (m), 1280 (m), 1186 (m), 1037 (w), 734 (m); δ_H (270 MHz, $CDCl_3$) 6.91 (1H, dt, *J* = 16, 5, C*H*=CHCO$_2$), 6.73 (1H, br s, N*H*), 5.97 (1H, dt, *J* = 16, 2, CH=C*H*CO$_2$), 5.96 (1H, s, Cl$_2$C*H*), 4.21 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 4.16–4.11 (2H, m, NHC*H*$_2$), 1.30 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 165.7, 164.3 (*C*ONH, *C*O$_2$Et), 142.0 (*C*H=CHCO$_2$), 122.5 (CH=*C*HCO$_2$), 66.1 (Cl*C*H), 60.7 (CO$_2$-*C*H$_2$), 40.7 (NH*C*H$_2$), 14.2 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 261 (^{37,37}M + NH_4^+, 12%), 259 (^{37,35}M + NH_4^+, 68), 257 (^{35,35}M + NH_4^+, 100), 240 (^{35,35}M + H^+, 4), 225 (17), 223 (51), 206 (6), 187 (37), 170 (19) (Found: ^{35,35}M + NH_4^+, 257.0462. C_8H_{11}-Cl_2NO_3 requires for ^{35,35}M + NH_4^+, 257.0640).

3,3-Dichloro-4-[(ethoxycarbonyl)methyl]pyrrolidin-2-one 10b. R_f 0.2 (petroleum ether–ethyl acetate, 1 : 1); ν_{max}/cm^{-1} ($CHCl_3$) 3432 (w), 3234 (w), 3133 (w), 2987 (w), 1735 (s), 1379 (w), 1330 (w), 1282 (m), 1184 (m), 1060 (w), 837 (m), 774 (w), 734 (w); δ_H (270 MHz, $CDCl_3$) 7.85 (1H, br s, N*H*), 4.19 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 3.72 (1H, m, C*H*CH$_2$CO$_2$), 3.29–3.15 (2H, m, NHC*H*$_2$), 2.97 (1H, dd, *J* = 16.5, 3, C*H*$_A$H$_B$CO$_2$), 2.70 (1H, dd, *J* = 16.5, 10, CH$_A$*H*$_B$CO$_2$), 1.30 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 170.4, 169.5 (*C*ONH, *C*O$_2$Et), 84.9 (Cl$_2$*C*), 61.2 (CO$_2$*C*H$_2$), 48.4 (*C*HCH$_2$CO$_2$), 44.6 (NH*C*H$_2$), 32.7 (*C*H$_2$-CO$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 261 (^{37,37}M + NH_4^+, 12%), 259 (^{37,35}M + NH_4^+, 65), 257 (^{35,35}M + NH_4^+, 100), 225 (27), 223 (81), 206 (18), 189 (10), 172 (6), 78 (5) (Found: ^{35,35}M + NH_4^+, 257.0461. $C_8H_{11}Cl_2NO_3$ requires for ^{35,35}M + NH_4^+, 257.0459).

***N*-Allyl-2-phenylethanamide 9c.** R_f 0.4 (petroleum ether–ethyl acetate, 1 : 1); ν_{max}/cm^{-1} ($CHCl_3$)[16] 3433 (w), 3008 (w), 2927 (w), 1666 (s), 1516 (m), 1242 (w), 741 (m), 710 (w); δ_H (270 MHz, $CDCl_3$)[16] 7.43–7.28 (5H, m, aromatics), 5.80 (1H, ddt, *J* = 17, 9.5, 5, C*H*=CH$_2$), 5.54 (1H, br s, N*H*), 5.12–5.04 (2H, m, CH=C*H*$_2$), 3.88 (2H, app. t, *J* = 7, NHC*H*$_2$), 3.63 (2H, s, PhC*H*$_2$); δ_C (67.5 MHz, $CDCl_3$)[16] 170.8 (*C*ONH), 134.8 (*C*=CH), 133.9 (*C*H=CH$_2$), 129.5, 129.0, 127.4 (*C*H=C), 116.0 (CH=*C*H$_2$), 43.8 (Ph*C*H$_2$), 41.8 (NH*C*H$_2$); *m*/*z* (CI, NH_3) 193 (M + NH_4^+, 7%), 176 (M + H^+, 100), 91 (8) (Found: M + H^+, 176.1072. $C_{11}H_{13}NO$ requires for M + H^+, 176.1075).

3-Phenyl-4-methylpyrrolidin-2-one 10c. (3*R**,4*S**) *Major diastereoisomer*; R_f 0.2 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3446 (w), 3008 (w), 2962 (w), 1701 (s), 721 (w); δ_H (270 MHz, $CDCl_3$) 7.41–7.13 (5H, m, aromatics), 6.74 (1H, br s, N*H*), 3.47 (1H, app. t, *J* = 9, NHC*H*$_A$H$_B$), 3.08 (1H, d, *J* = 10.5, PhC*H*), 2.97 (1H, app. t, *J* = 9, NHCH$_A$*H*$_B$), 2.45 (1H, m, C*H*CH$_3$), 1.08 (3H, d, *J* = 7, CHC*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 178.7 (*C*ONH), 138.1 (*C*=CH), 128.7, 128.6, 127.2 (*C*H=C), 56.2 (Ph*C*H), 47.9 (NH*C*H$_2$), 40.1 (*C*HCH$_3$), 17.3 (CH*C*H$_3$); *m*/*z* (EI) 175 (M$^+$, 84%), 160 (6), 132 (20), 127 (100), 91 (62), 77 (7) (Found: M$^+$, 175.0994. $C_{11}H_{13}NO$ requires for M$^+$, 175.0971).

(3*R**,4*R**) *Minor diastereoisomer*: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 3.64

(1H, d, J = 8.5, PhC*H*), 2.89 (1H, m, C*H*CH_3), 0.65 (3H, d, J = 7, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 185.0 (*C*ONH), 133.8 (*C*=CH), 129.3, 128.5, 127.0 (*C*H=C), 57.5 (Ph*C*H), 45.0 (NHCH_2), 41.3 (*C*HCH_3), 15.0 (CH*C*H_3).

Ethyl (*E*)-4-(phenylethanamido)but-2-enoate 9d. R_f 0.5 (dichloromethane–ethyl acetate, 1:1); ν_{max}/cm^{-1} ($CHCl_3$) 3433 (w), 2926 (s), 2854 (w), 1727 (s), 1662 (m), 1604 (m), 1261 (m), 756 (s); δ_H (270 MHz, $CDCl_3$) 7.32–7.20 (5H, m, aromatics), 6.73 (1H, dt, J = 16, 5, C*H*=CHCO$_2$), 5.70 (1H, d, J = 16, CH=C*H*CO$_2$), 5.42 (1H, br s, N*H*), 4.10 (2H, q, J = 7, CO$_2$CH_2), 3.96–3.90 (2H, m, NHCH_2), 3.81 (2H, s, PhCH_2), 1.28 (3H, t, J = 7, CO$_2$CH$_2$CH_3); δ_C (67.5 MHz, $CDCl_3$) 176.8, 171.3 (*C*ONH, *C*O$_2$Et), 143.5 (*C*H=CHCO$_2$), 137.3 (*C*=CH), 129.5, 129.2, 127.5 (*C*H=C), 121.8 (CH=*C*HCO$_2$), 60.5 (CO$_2$CH_2), 40.2 (NHCH_2), 29.7 (PhCH_2), 14.2 (CO$_2$CH$_2$CH_3); *m*/*z* (CI, NH_3) 265 (M + NH_4^+, 7%), 248 (M + H^+, 28), 223 (7), 195 (10), 178 (82), 164 (7), 153 (11), 136 (8), 121 (20), 108 (9) (Found: M + H^+, 248.1283. $C_{14}H_{17}NO_3$ requires for M + H^+, 248.1287).

3-Phenyl-4-[(ethoxycarbonyl)methyl]pyrrolidin-2-one 10d. (3*R**,4*S**) *Major diastereoisomer*: R_f 0.2 (dichloromethane–ethyl acetate, 1:1); ν_{max}/cm^{-1} ($CHCl_3$) 3437 (w), 3008 (w), 1705 (s), 1237 (w), 702 (w); δ_H (270 MHz, $CDCl_3$) 7.32–7.05 (5H, m, aromatics), 6.50 (1H, br s, N*H*), 3.99 (2H, q, J = 7, CO$_2$CH_2), 3.72 (1H, m, NHCH_AH$_B$), 3.22 (1H, d, J = 10, PhC*H*), 3.15–3.06 (2H, m, NHCH$_A$$H_B$ and C*H*CH$_2$CO$_2$), 2.54 (1H, dd, J = 16, 5, CH_AH$_B$CO$_2$), 2.33 (1H, dd, J = 16, 7, CH$_A$$H_BCO_2$), 1.18–1.09 (3H, m, CO$_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 177.4, 171.3 (*C*ONH, *C*O$_2$Et), 137.3 (*C*=CH), 129.0, 128.8, 127.5 (*C*H=C), 60.7 (CO$_2$CH_2), 53.3 (Ph*C*H), 46.0 (NH*C*H$_2$), 41.2 (*C*HCH$_2$CO$_2$), 37.1 (*C*H$_2$CO$_2$), 14.1 (CO$_2$CH$_2$CH_3); *m*/*z* (CI, NH_3) 265 (M + NH_4^+, 30%), 248 (M + H^+, 100), 160 (6) (Found: M + H^+, 248.1282. $C_{14}H_{17}NO_3$ requires for M + H^+, 248.1287).

(3*R**,4*R**) *Minor diastereoisomer*: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.32–7.05 (5H, m, aromatics), 6.54 (1H, br s, N*H*), 3.99 (2H, q, J = 7, CO$_2$CH_2), 3.66–3.59 (2H, m, NHCH_2), 3.64 (1H, d, J = 9, PhC*H*), 2.81 (1H, m, C*H*CH$_2$), 2.00–1.97 (2H, m, CH_2CO$_2$); δ_C (67.5 MHz, $CDCl_3$) 178.2, 171.8 (*C*ONH, *C*O$_2$Et), 135.0 (*C*=CH), 129.0, 128.8, 127.4 (*C*H=C), 60.5 (CO$_2$CH_2), 51.0 (Ph*C*H), 46.0 (NH*C*H$_2$), 36.2 (*C*HCH$_2$CO$_2$), 34.6 (*C*H$_2$CO$_2$), 14.1 (CO$_2$CH$_2$CH_3).

Ethyl (*E*)-4-(2-hydroxy-2-methylpropanamido)but-2-enoate 9e. R_f 0.3 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3380 (br, m), 2977 (m), 2977 (m), 2930 (m), 1721 (s), 1656 (s), 1526 (m); δ_H (400 MHz, $CDCl_3$) 7.01 (1H, br s, N*H*), 6.91 (1H, dt, J = 16, 5, C*H*=CHCO$_2$), 5.90 (1H, d, J = 16, CH=C*H*CO$_2$), 4.19 (2H, q, J = 7, CO$_2$CH_2), 4.07–4.04 (2H, m, NHCH_2), 2.47 (1H, br s, O*H*), 1.48 (6H, s, 2 × CH_3), 1.27 (3H, t, J = 7, CO$_2$CH$_2$CH_3); δ_C (67.5 MHz; $CDCl_3$) 176.4, 166.0 (*C*ONH, *C*O$_2$Et), 143.9 (*C*H=CHCO$_2$), 121.8 (CH=*C*HCO$_2$), 73.9 (Me$_2$*C*OH), 60.6 (CO$_2$CH_2), 39.8 (NHCH_2), 28.0 (2 × CH_3), 14.2 (CO$_2$CH$_2$CH_3); *m*/*z* (CI, NH_3) 233 (M + NH_4^+, 55%), 216 (M + H^+, 100).

3,3-Dimethyl-4-[(ethoxycarbonyl)methyl]pyrrolidin-2-one 10e. R_f 0.2 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3328 (m), 2966 (m), 2931 (s), 1732 (s), 1698 (s); δ_H (400 MHz, $CDCl_3$) 6.51 (1H, br s, N*H*), 4.15 (2H, q, J = 7, CO$_2$CH_2), 3.54 (1H, app. t, J = 8, NHCH_AH$_B$), 2.99 (1H, app. t, J = 9.5, NHCH$_A$$H_B$), 2.52 (1H, m, C*H*CH$_2CO_2$), 2.49 (1H, dd, J = 16, 5, CH_AH$_B$CO$_2$), 2.31 (1H, dd, J = 16, 9.5, CH$_A$$H_BCO_2$), 1.27 (3H, t, J = 7, CO$_2$CH$_2$CH_3), 1.16 (3H, s, CH_3) and 1.10 (3H, s, CH_3); δ_C (67.5 MHz; $CDCl_3$) 182.7, 172.2 (*C*ONH, *C*O$_2$Et), 60.8 (CO$_2$CH_2), 44.7 (NH*C*H$_2$), 42.4 (*C*HCH$_2$CO$_2$), 42.0 (*C*CH$_3$), 33.6 (*C*H$_2$CO$_2$), 23.4 (*C*H$_3$), 18.7 (*C*H$_3$), 14.2 (CO$_2$CH$_2$CH_3); *m*/*z* (CI, NH_3) 217 (M + NH_4^+, 30%), 200 (M + H^+, 100) (Found: M + NH_4^+, 217.1549. $C_{10}H_{17}NO_3$ requires for M + NH_4^+, 217.1552).

Ethyl (*E*)-4-(chloroethanamido)but-2-enoate 9f. R_f 0.4 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3427 (m), 3006 (m), 2929 (m), 1714 (s), 1679 (s), 1529 (s), 1413 (m), 1371 (m), 1279 (s), 1185 (s), 1037 (m), 733 (m), 708 (m); δ_H (270 MHz, $CDCl_3$) 6.99 (1H, br s, N*H*), 6.91 (1H, dt, J = 16, 5, C*H*=CHCO$_2$), 5.94 (1H, dt, J = 16, 2, CH=C*H*CO$_2$), 4.21 (2H, q, J = 7, CO$_2$CH_2), 4.16–4.06 (2H, m, NHCH_2), 4.11 (2H, s, ClCH_2), 1.29 (3H, t, J = 7, CO$_2$CH$_2$CH_3); δ_C (67.5 MHz, $CDCl_3$) 166.0, 165.7 (*C*ONH, *C*O$_2$Et), 142.7 (*C*H=CHCO$_2$), 122.1 (CH=*C*HCO$_2$), 60.4 (CO$_2$CH_2), 42.4 (ClCH_2), 40.2 (NHCH_2), 14.9 (CO$_2$CH$_2$CH_3); *m*/*z* (CI, NH_3) 225 (^{37}M + NH_4^+, 18%), 223 (^{35}M + NH_4^+, 56), 208 (^{37}M + H^+, 33), 206 (^{35}M + H^+, 100), 189 (14), 172 (38), 56 (38) (Found: ^{35}M + H^+, 206.0578. $C_8H_{12}ClNO_3$ requires for ^{35}M + H^+, 206.0584).

3-Chloro-4-[(ethoxycarbonyl)methyl]pyrrolidin-2-one 10f. (3*R**,4*S**) *Major diastereoisomer*: R_f 0.3 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3437 (w), 3006 (w), 1724 (br, s), 1600 (w), 1425 (w), 1380 (w), 1194 (w), 1025 (w), 908 (m); δ_H (270 MHz, $CDCl_3$) 7.24 (1H, br s, N*H*), 4.17 (2H, q, J = 7, CO$_2$CH_2), 4.15 (1H, m, C*H*Cl), 3.72 (1H, app. t, J = 9, NHCH_AH$_B$), 3.20 (1H, dd, J = 13, 9, NHCH$_A$$H_B$), 2.94 (1H, m, C*H*CH$_2CO_2$), 2.78 (1H, m, C$H_AH_BCO_2$), 2.52 (1H, dd, J = 16, 7.5, CH$_A$$H_BCO_2$), 1.27 (3H, t, J = 7, CO$_2$CH$_2$CH_3); δ_C (67.5 MHz, $CDCl_3$) 176.1, 171.1 (*C*ONH, *C*O$_2$Et), 60.1 (CO$_2$CH_2), 58.5 (Cl*C*H), 45.2 (NHCH_2), 42.1 (*C*HCH$_2$CO$_2$), 35.7 (*C*H$_2$CO$_2$), 14.2 (CO$_2$CH$_2$-CH_3); *m*/*z* (CI, NH_3) 225 (^{37}M + NH_4^+, 34%), 223 (^{35}M + NH_4^+, 100), 208 (^{37}M + H^+, 17), 206 (^{35}M + H^+, 52), 170 (15) (Found: ^{35}M + NH_4^+, 223.0849. $C_8H_{12}ClNO_3$ requires for ^{35}M + NH_4^+, 223.0849).

(3*R**,4*R**) *Minor diastereoisomer*: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.14 (1H, br s, NH), 4.43 (1H, d, J = 7, ClCH), 3.54 (1H, dd, J = 10, 8.5, NHCH_AH$_B$), 3.16 (1H, m, NCH$_A$$H_B$), 3.06 (1H, m, C*H*CH$_2CO_2$), 2.80 (1H, m, C$H_AH_BCO_2$); δ_C (67.5 MHz, $CDCl_3$) 174.1, 170.7 (*C*ONH, *C*O$_2$Et), 58.3 (Cl*C*H), 37.1 (*C*HCH$_2$CO$_2$), 33.3 (*C*H$_2$CO$_2$).

4-(Chloroethanamido)-1-phenylbutan-1-one 13. Oil; R_f 0.55 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3423 (w), 3006 (w), 2960 (w), 1677 (s), 1535 (m), 1448 (w), 1411 (w), 1363 (w), 1259 (w), 1214 (w), 908 (w); δ_H (270 MHz, $CDCl_3$) 8.02–7.93 (2H, m, aromatics), 7.60–7.43 (3H, m, aromatics), 6.84 (1H, br s, NH), 4.02 (2H, s, ClCH_2), 3.42 (2H, app. q, J = 6.5, NHCH_2), 3.07 (2H, t, J = 7, CH_2COPh), 2.03 (2H, app, quintet, J = 7, CH$_2$CH_2CH$_2$); δ_C (67.5 MHz, $CDCl_3$) 199.7 (*C*OPh), 166.3 (*C*ONH), 136.6 (*C*=CH), 133.3, 128.7, 128.3 (*C*H=C), 42.6, 39.6 (Cl*C*H$_2$, NH*C*H$_2$), 35.8 (CH$_2$*C*H$_2$CH$_2$), 23.5 (*C*H$_2$COPh); *m*/*z* (CI, NH_3) 259 (^{37}M + NH_4^+, 19%), 257 (^{35}M + NH_4^+, 54), 242 (^{37}M + H^+, 33), 240 (^{35}M + H^+, 100), 223 (21), 206 (100), 146 (6), 105 (5) (Found: ^{35}M + H^+, 240.0785. $C_{12}H_{14}ClNO_2$ requires for ^{35}M + H^+, 240.0785).

General procedure for deprotection and acylation of 14a–b

A solution of the carbamate **14a**–**b** (0.45–0.73 g, 1.51–2.56 mmol) in dichloromethane (7–8 cm^3) at 0 °C was treated with trifluoroacetic acid (1.2–2.0 cm^3, 15.1–25.6 mmol) before allowing to warm to room temp. and stirring overnight. The solvent was removed *in vacuo* to give the amine salt (0.45–0.74 g, 95–98%) as an oil. A suspension of the salt (0.07–0.27 g, 0.21–0.88 mmol) in dichloromethane (3–4 cm^3) at 0 °C was treated with triethylamine (0.03–0.13 cm^3, 0.23–0.96 mmol) followed by the dropwise addition of the acid chloride (0.04–0.1 cm^3, 0.23–0.96 mmol) and the reaction was stirred at 0 °C for 0.5 h before

warming to room temp. and stirring for a further 3–6 h. The solution was washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford crude product which was purified by column chromatography (silica) to give amide **15**, **16a**–**c** (55–78%) as oils.

Ethyl (*E*)-4-(2-chloro-2-phenylethanamido)-5-methylhex-2-enoate 15. R_f 0.3 (petroleum ether–ethyl acetate, 3:1); $[\alpha]_D^{20}$ −21.7 (*c* 0.71, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3417 (w), 3014 (w), 2996 (w), 1712 (s), 1678 (s), 1516 (m), 1303 (m), 1188 (m), 786 (m), 750 (s), 727 (s); δ_H (270 MHz, $CDCl_3$) (mixture of conformers) 7.46–7.33 (5H, m, aromatics), 6.87 (1H, m, C*H*=CHCO$_2$), 5.92, 5.86 (1H, 2 × dd, *J* = 16, 2, CH=C*H*CO$_2$), 5.43, 5.42 (1H, 2 × s, PhC*H*), 4.49 (1H, m, NHC*H*), 4.23, 4.19 (2H, 2 × q, *J* = 7, CO$_2$C*H*$_2$), 1.94 (1H, m, C*H*Me$_2$), 1.28, 1.23 (3H, 2 × t, *J* = 7, CO$_2$CH$_2$C*H*$_3$), 0.96 (3H, d, *J* = 6, CH(C*H*$_3$)$_A$), 0.90 (3H, d, *J* = 6, CH(C*H*$_3$)$_B$); δ_C (67.5 MHz, $CDCl_3$) (mixture of conformers) 167.5, 166.3 (*C*ONH, *C*O$_2$Et), 146.1, 146.0 (*C*H=CHCO$_2$), 137.2, 137.1 (*C*=CH), 129.5, 129.2, 128.2, 128.0 (*C*H=C), 122.6, 122.5 (CH=*C*HCO$_2$), 62.1, 62.0 (Ph*C*H), 60.9, 60.7 (CO$_2$*C*H$_2$), 56.2, 56.1 (NH*C*H), 32.4 (*C*HMe$_2$), 19.3, 19.2 (CH*C*H$_3$), 18.4, 18.0 (CH*C*H$_3$), 14.6 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 326 ($^{37}M + H^+$, 36), 324 ($^{35}M + H^+$, 100), 290 (54), 246 (7), 202 (11), 155 (11), 125 (13) (Found: $^{35}M + H^+$, 324.1363. $C_{17}H_{22}ClNO_3$ requires for $^{35}M + H^+$, 324.1366).

(*E*)-1-(2-Chloro-2-phenylethanamido)-1-(ethoxycarbonylpropenyl)cyclohexane 16a. R_f 0.2 (petroleum ether–ethyl acetate, 4:1); ν_{max}/cm^{-1} ($CHCl_3$) 3413 (w), 2983 (w), 2937 (w), 1708 (s), 1682 (s), 1513 (w), 1452 (w), 1307 (w), 1278 (w), 1217 (w), 1162 (w); δ_H (270 MHz, $CDCl_3$) 7.40–7.25 (5H, m, aromatics), 6.87 (1H, d, *J* = 16, C*H*=CHCO$_2$), 6.45 (1H, br s, N*H*), 5.73 (1H, d, *J* = 16, CH=C*H*CO$_2$), 5.26 (1H, s, PhC*H*), 4.08 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 2.09–2.00 (2H, m, cyclohexyl), 1.54–1.21 (8H, m, cyclohexyl), 1.19 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 166.5, 166.2 (*C*ONH, *C*O$_2$Et), 151.2 (*C*H=CHCO$_2$), 136.8 (*C*=CH), 129.0, 128.9, 127.6 (*C*H=C), 119.4 (CH=*C*HCO$_2$), 62.0 (Ph*C*H), 60.4 (CO$_2$*C*H$_2$), 56.4 (*C*NH), 34.5, 34.0, 25.0, 21.3 (cyclohexyl *C*H$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 350 ($^{35}M + H^+$, 8%), 316 (100), 300(9), 270 (9), 228 (10), 181 (6), 152 (6), 136 (5) (Found: $^{35}M + H^+$, 350.1529. $C_{19}H_{24}ClNO_3$ requires for $^{35}M + H^+$, 350.1523).

(*E*)-1-(2-Chloropropanamido)-1-(ethoxycarbonylpropenyl)cyclohexane 16b. R_f 0.35 (petroleum ether–ethyl acetate, 3:1); ν_{max}/cm^{-1} ($CHCl_3$) 3413 (w), 2939 (m), 1709 (s), 1680 (s), 1518 (s), 1450 (w), 1369 (w), 1305 (m), 1267 (w), 1182 (w); δ_H (270 MHz, $CDCl_3$) 6.96 (1H, d, *J* = 16, C*H*=CHCO$_2$), 6.58 (1H, br s, N*H*), 5.83 (1H, d, *J* = 16, CH=C*H*CO$_2$), 4.39 (1H, q, *J* = 7, C*H*CH$_3$), 4.18 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 2.18–2.04 (2H, m, cyclohexyl), 1.73 (3H, d, *J* = 7, CHC*H*$_3$), 1.66–1.29 (8H, m, cyclohexyl), 1.26 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 168.2, 166.5 (*C*ONH, *C*O$_2$Et), 151.5 (*C*H=CHCO$_2$), 119.0 (CH=*C*HCO$_2$), 60.3 (CO$_2$*C*H$_2$), 56.0 (*C*NH), 55.9 (*C*HCH$_3$), 34.2, 33.9, 24.9 (cyclohexyl *C*H$_2$), 22.4 (CH*C*H$_3$), 21.2 (cyclohexyl *C*H$_2$), 14.0 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 307 ($^{37}M + NH_4^+$, 15%), 305 ($^{35}M + NH_4^+$, 45), 290 ($^{37}M + H^+$, 18), 288 ($^{35}M + H^+$, 50), 254 (100), 238 (15), 208 (6), 196 (5), 181 (8) (Found: $^{35}M + H^+$, 288.1358. $C_{14}H_{22}ClNO_3$ requires for $^{35}M + H^+$, 288.1366).

(*E*)-1-(Trichloroethanamido)-1-(ethoxycarbonylpropenyl)cyclohexane 16c. R_f 0.3 (petroleum ether–ethyl acetate, 4:1); ν_{max}/cm^{-1} ($CHCl_3$) 3425 (m), 3025 (m), 2939 (m), 1722 (s), 1656 (m), 1509 (m), 1450 (m), 1369 (w), 1307 (m), 1272 (w), 1236 (w), 1176 (m), 1039 (w), 794 (w), 733 (s); δ_H (270 MHz, $CDCl_3$) 6.90 (1H, d, *J* = 16, C*H*=CHCO$_2$), 6.50 (1H, br s, N*H*), 5.85 (1H, d, *J* = 16, CH=C*H*CO$_2$), 4.11 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 2.18–2.10 (2H, m, cyclohexyl), 1.67–1.56 (5H, m, cyclohexyl), 1.45–1.30 (3H, m, cyclohexyl), 1.26 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 166.3, 160.0, (*C*ONH, *C*O$_2$Et), 149.9, 149.5 (*C*H=CHCO$_2$), 120.0, 119.7 (*C*H=CHCO$_2$), 92.9 (Cl$_3$*C*), 60.5 (CO$_2$*C*H$_2$), 57.2 (*C*NH), 34.0, 24.8, 24.7, 21.2, 21.1 (cyclohexyl *C*H$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 363 ($^{37,37,35}M + NH_4^+$, 5%), 361 ($^{37,35,35}M + NH_4^+$, 19), 359 ($^{35,35,35}M + NH_4^+$, 20), 327 (10), 325 (15), 291 (11), 274 (31), 240 (100), 152 (23) (Found: $^{35,35,35}M + NH_4^+$, 359.0696. $C_{13}H_{18}Cl_3NO_3$ requires for $^{35,35,35}M + NH_4^+$, 359.0696).

Radical cyclisation of alkene 15

Following the general procedure, alkene **15** (124 mg, 0.38 mmol) in degassed toluene (15 cm^3) was treated with tributyltin hydride (122 mg, 0.42 mmol) and azobisisobutyronitrile (13 mg, 0.08 mmol) in toluene (30 cm^3) over a 1 h addition period, and the reaction mixture heated at reflux for a further 18 h. Column chromatography (ethyl acetate–petroleum ether, 2:1) afforded 3-phenyl-4-(ethoxycarbonylmethyl)-5-isopropylpyrrolidin-2-ones **17**, **18** and **19** (62 mg, 56%) as colourless oils in a ratio of 9.0:4.0:1, together with simple reduced product **20** (4 mg, 4%) as a colourless oil.

(3*R*,4*R*,5*S*) *Major diastereoisomer* **17**; R_f 0.2 (ethyl acetate–petroleum ether, 2:1); ν_{max}/cm^{-1} ($CHCl_3$) 3424 (vw), 3052 (w), 2985 (m), 1709 (s), 1422 (w), 1264 (s), 1227 (w), 896 (w); δ_H (270 MHz, $CDCl_3$) 7.37–7.18 (5H, m, aromatics), 6.96 (1H, br s, N*H*), 4.02–3.90 (2H, m, CO$_2$C*H*$_2$), 3.51 (1H, d, *J* = 9, PhC*H*), 3.28 (1H, dd, *J* = 11.5, 6.5, NHC*H*), 2.65–2.48 (3H, m, C*H*$_2$CO$_2$, C*H*CH$_2$CO$_2$), 1.79 (1H, app. octet, *J* = 6, C*H*Me$_2$), 1.13 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$), 1.00 (3H, d, *J* = 7, CH(C*H*$_3$)$_A$), 0.96 (3H, d, *J* = 7, CH(C*H*$_3$)$_B$); δ_C (67.5 MHz, $CDCl_3$) 176.9, 171.3 (*C*ONH, *C*O$_2$Et), 138.5 (*C*=CH), 128.7, 128.6, 128.5, 127.2 (*C*H=C), 63.2 (Ph*C*H), 60.6 (CO$_2$*C*H$_2$), 54.6 (NH*C*H), 44.0 (*C*HCH$_2$CO$_2$), 38.0 (*C*H$_2$CO$_2$), 31.3 (*C*HMe$_2$), 19.9, 17.1 (CH(*C*H$_3$)$_2$), 14.0 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 290 (M + H$^+$, 100%), 274 (9), 246 (6), 214 (21), 202 (17), 126 (12) (Found: M + H$^+$, 290.1757. $C_{17}H_{23}NO_3$ requires for M + H$^+$, 290.1756).

(3*S*,4*R*,5*S*) *Minor diastereoisomer* **18**; R_f 0.25 (ethyl acetate–petroleum ether, 2:1); ν_{max}/cm^{-1} ($CHCl_3$) 3433 (w), 2966 (m), 2931 (m), 1726 (s), 1695 (s), 1466 (w), 1381 (w), 1313 (w), 1242 (m), 1172 (m), 1030 (w), 908 (m), 702 (m); δ_H (270 MHz, $CDCl_3$) 7.40–7.10 (5H, m, aromatics), 4.00 (1H, d, *J* = 9, PhC*H*), 3.99 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 3.19 (1H, app. t, *J* = 5, NHC*H*), 3.01–2.91 (1H, m, C*H*CH$_2$CO$_2$), 2.18 (1H, dd, *J* = 16.5, 8, C*H*$_A$H$_B$CO$_2$), 1.92 (1H, dd, *J* = 16.5, 7.5, CH$_A$*H*$_B$CO$_2$), 1.90–1.78 (1H, m, C*H*Me$_2$), 1.16 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$), 1.03 (3H, d, *J* = 7, CH(C*H*$_3$)$_A$), 0.98 (3H, d, *J* = 7, CH(C*H*$_3$)$_B$); δ_C (67.5 MHz, $CDCl_3$) 171.9, 166.3 (*C*ONH, *C*O$_2$Et), 135.1 (*C*=CH), 129.6, 128.6, 127.3 (*C*H=C), 63.8 (Ph*C*H), 60.5 (CO$_2$*C*H$_2$), 47.0 (NH*C*H), 38.9 (*C*HCH$_2$CO$_2$), 35.6 (*C*H$_2$CO$_2$), 31.6 (*C*HMe$_2$), 19.7, 17.7 (CH(*C*H$_3$)$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 290 (M + H$^+$, 100%), 274 (14), 246 (11), 214 (20), 202 (23), 186 (8), 142 (5), 126 (21) (Found: M + H$^+$, 290.1754. $C_{17}H_{23}NO_3$ requires for M + H$^+$, 290.1756).

(3*S*,4*S*,5*S*) *Minor diastereoisomer* **19**; R_f 0.25 (ethyl acetate–petroleum ether, 2:1); the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.40–7.10 (5H, m, aromatics), 3.73–3.63 (1H, m, NHC*H*), 3.40 (1H, d, *J* = 10, PhC*H*), 2.63–2.51 (1H, m, C*H*CH$_2$CO$_2$), 1.70–1.61 (1H, m, C*H*Me$_2$).

Phenylethanamide **20**; R_f 0.5 (ethyl acetate–petroleum ether, 2:1); δ_H (270 MHz, $CDCl_3$) 7.40–7.25 (5H, m, aromatics), 6.76 (1H, dd, *J* = 15.5, 6.5, C*H*=CHCO$_2$), 5.88 (1H, br s, N*H*), 5.73 (1H, dd, *J* = 15.5, 1.5, CH=C*H*CO$_2$), 4.53 (1H, app dd, *J* = 9, 5, NC*H*), 4.17 (2H, q, *J* = 7, CO$_2$C*H*$_2$), 3.60 (2H, s, PhC*H*$_2$), 2.10–2.00 (1H, m, C*H*Me$_2$), 1.28 (3H, t, *J* = 7, CO$_2$CH$_2$C*H*$_3$), 0.85, 0.76 (3H, 2 × d, *J* = 7, CHC*H*$_3$), 0.82, 0.74 (3H, 2 × d, *J* = 7, CHC*H*$_3$).

Radical cyclisation of alkene 16a

Following the general procedure, the alkene **16a** (54 mg, 0.15 mmol) in degassed toluene (7 cm^3) was treated with tributyltin hydride (54 mg, 0.18 mmol) and azobisisobutyronitrile (5 mg, 0.03 mmol) in toluene (14 cm^3) over a 1 h addition period, and the reaction mixture heated at reflux for a further 18 h. Column chromatography (petroleum ether–ethyl acetate, 1:1, followed by ethyl acetate) afforded the inseparable pyrrolidinones **21a** and **22a** (33 mg, 68%) as an off-white solid in a ratio of 3.7:1 (from the ^{1}H NMR spectrum), together with simple reduced product **23a** (2 mg, 3%) as a colourless oil.

(3*R**,4*S**) *Major diastereoisomer* **21a**; R_f 0.5 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3429 (m), 2937 (m), 1726 (s), 1695 (s), 1454 (w), 1403 (w), 1305 (w), 1261 (w), 1228 (w), 1028 (w); δ_H (270 MHz, $CDCl_3$) 7.37–7.11 (5H, m, aromatics), 6.91 (1H, br s, N*H*), 3.87–3.70 (2H, m, CO_2CH_2), 3.44 (1H, d, J = 12.5, PhC*H*), 2.68–2.59 (1H, dt, J = 15, 7.5, C*H*CH_2CO_2), 2.49 (1H, dd, J = 14.5, 7, C$H_AH_BCO_2$), 2.36 (1H, dd, J = 14.5, 7.5, $CH_AH_BCO_2$), 1.76–1.57 (6H, m, cyclohexyl), 1.48–1.27 (4H, m, cyclohexyl), 1.08 (3H, t, J = 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 175.6, 171.7 (*C*ONH, *C*O_2Et), 137.2 (*C*=CH), 129.0, 128.4, 127.4 (*C*H=C), 60.5 (CO_2CH_2), 59.1 (*C*NH), 53.5 (Ph*C*H), 51.7 (*C*HCH_2CO_2), 37.1 (cyclohexyl *C*H_2), 34.2 (*C*H_2CO_2), 32.3, 25.3, 23.3, 21.9 (cyclohexyl *C*H_2), 13.9 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 316 (M + H^+, 100%), 272 (5), 228 (17), 99 (6) (Found: M + H^+, 316.1909. $C_{19}H_{25}NO_3$ requires for M + H^+, 316.1913).

(3*R**,4*R**) *Minor diastereoisomer* **22a**; the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.37–7.11 (5H, m, aromatics), 6.86 (1H, br s, N*H*), 4.12 (1H, d, J = 9.5, PhC*H*), 4.03–3.92 (2H, m, CO_2CH_2), 2.97 (1H, m, C*H*CH_2CO_2), 2.23 (1H, dd, J = 16.5, 5.5, C$H_AH_BCO_2$), 1.95 (1H, dd, J = 16.5, 9.5, $CH_AH_BCO_2$), 1.17 (3H, t, J = 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 176.4, 172.5 (*C*ONH, *C*O_2Et), 135.7 (*C*=CH), 130.0, 128.6, 127.2 (*C*H=C), 60.5 (CO_2CH_2), 59.9 (*C*NH), 51.1 (Ph*C*H), 45.7 (*C*HCH_2CO_2), 38.3, 33.9 (cyclohexyl *C*H_2), 31.7 (*C*H_2CO_2), 25.2, 22.4 (cyclohexyl *C*H_2), 13.9 ($CO_2CH_2CH_3$).

Phenylethanamide **23a**; R_f 0.4 (petroleum ether–ethyl acetate, 1:1); the presence of this was indicated by ^{1}H NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.42–7.22 (5H, m, aromatics), 6.93 (1H, d, J = 16, C*H*=CHCO_2), 5.77 (1H, d, J = 16, CH=C*H*CO_2), 5.19 (1H, br s, N*H*), 4.16 (2H, q, J = 7, CO_2CH_2), 3.58 (2H, s, PhCH_2).

Radical cyclisation of alkene 16b

Following the general procedure, alkene **16b** (154 mg, 0.53 mmol) in degassed toluene (22 cm^3) was treated with tributyltin hydride (184 mg, 0.63 mmol) and azobisisobutyronitrile (17 mg, 0.11 mmol) in toluene (44 cm^3) over a 1 h addition period, and the reaction mixture heated at reflux for a further 18 h. Column chromatography (ethyl acetate–petroleum ether, 2:1) afforded the inseparable pyrrolidinones **21b** and **22b** (103 mg, 76%) as a white solid in a ratio of 1.8:1 (from the ^{1}H NMR spectrum), together with simple reduced product **23b** (9 mg, 4%) as a colourless oil.

(3*R**,4*R**) *Major diastereoisomer* **21b**; R_f 0.2 (ethyl acetate–petroleum ether, 2:1); ν_{max}/cm^{-1} ($CHCl_3$) 3433 (m), 3020 (s), 2935 (s), 2856 (m), 1728 (s), 1691 (s), 1454 (w), 1404 (w), 1381 (w), 1305 (m), 1240 (m), 1165 (m), 1026 (w); δ_H (270 MHz, $CDCl_3$) 7.71 (1H, br s, N*H*), 4.16 (2H, q, J = 7, CO_2CH_2), 2.48 (1H, dd, J = 15, 8, C$H_AH_BCO_2$), 2.34 (1H, dd, J = 15, 8, $CH_AH_BCO_2$), 2.23 (1H, dq, J = 11, 7, C*H*CH_3), 2.11 (1H, dt, J = 11, 7, C*H*CH_2CO_2), 1.75–1.32 (10H, m, cyclohexyl), 1.26 (3H, t, J = 7, $CO_2CH_2CH_3$), 1.16 (3H, d, J = 7, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 177.8, 172.3 (*C*ONH, *C*O_2Et), 60.5 (CO_2CH_2), 59.5 (*C*NH), 50.4 (*C*HCH_3), 41.1 (*C*HCH_2CO_2), 37.0 (cyclohexyl *C*H_2), 34.3 (*C*H_2CO_2), 32.3, 25.3, 22.8, 21.6 (cyclohexyl *C*H_2), 14.3 (CH*C*H_3), 14.0 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 254 (M + H^+, 100%), 210 (7) (Found: M + H^+, 254.1751. $C_{14}H_{23}NO_3$ requires for M + H^+, 254.1756).

(3*R**,4*S**) *Minor diastereoisomer* **22b**; the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.88 (1H, br s, N*H*), 4.17 (2H, q, J = 7, CO_2CH_2), 2.73 (1H, app. quintet, J = 8, C*H*CH_3), 2.59 (1H, app. q, J = 8, C*H*CH_2CO_2), 2.40 (2H, d, J = 8, CH_2CO_2), 17.5–1.32 (10H, m, cyclohexyl), 1.28 (3H, t, J = 7, $CO_2CH_2CH_3$), 1.13 (3H, d, J = 8, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 179.3, 172.3 (*C*ONH, *C*O_2Et), 60.5 (CO_2CH_2), 60.0 (*C*NH), 44.2 (*C*HCH_2CO_2), 39.0 (*C*HCH_3), 37.5, 34.5 (cyclohexyl *C*H_2), 30.6 (*C*H_2CO_2), 25.2, 21.9 (cyclohexyl *C*H_2), 14.0 ($CO_2CH_2CH_3$), 12.6 (CH*C*H_3).

Propanamide **23b**; R_f 0.4 (ethyl acetate–petroleum ether, 2:1); ν_{max}/cm^{-1} ($CDCl_3$) 3438 (w), 3008 (m), 2937 (s), 2858 (m), 1709 (s), 1679 (s), 1502 (s), 1450 (w), 1305 (m), 1272 (m), 1228 (m), 1180 (m), 727 (s); δ_H (270 MHz, $CDCl_3$) 6.98 (1H, d, J = 16, C*H*=CHCO_2), 5.83 (1H, d, J = 16, CH=C*H*CO_2), 5.29 (1H, br s, N*H*), 4.17 (2H, q, J = 7, CO_2CH_2), 2.22 (2H, q, J = 7.5, MeCH_2), 2.12–2.05 (2H, m, cyclohexyl), 1.70–1.42 (8H, m, cyclohexyl), 1.28 (3H, t, J = 7, $CO_2CH_2CH_3$), 1.16 (3H, t, J = 7.5, $COCH_2CH_3$).

Radical cyclisation of alkene 16c

Following the general procedure, alkene **16c** (145 mg, 0.44 mmol) in degassed toluene (19 cm^3) was treated with tributyltin hydride (392 mg, 1.35 mmol) and azobisisobutyronitrile (15 mg, 0.09 mmol). Column chromatography (ethyl acetate–petroleum ether, 3:1 then ethyl acetate) afforded pyrrolidinone **24** (59 mg, 58%) as a white solid together with unreacted starting material (42 mg); mp 143–146 °C; R_f 0.3 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3425 (w), 2937 (s), 2862 (w), 1728 (m), 1691 (s), 1602 (w), 1452 (w), 1402 (w), 1306 (w), 1242 (w), 1176 (w), 1026 (w); δ_H (500 MHz, $CDCl_3$) 7.36 (1H, br s, N*H*), 4.19 (2H, q, J = 7, CO_2CH_2), 2.63 (1H, dd, J = 16.5, 8, NHCOCH_AH_B or C$H_AH_BCO_2$), 2.53–2.49 (2H, m, C*H*CH_2CO_2, NHCOCH_AH_B or C$H_AH_BCO_2$), 2.33 (1H, dd, J = 16, 11.5, NHCOCH_AH_B or $CH_AH_BCO_2$), 2.18 (1H, dd, J = 16.5, 9, NHCOCH_AH_B or $CH_AH_BCO_2$), 1.75–1.69 (3H, m, cyclohexyl), 1.61–1.58 (3H, m, cyclohexyl), 1.46–1.35 (4H, m, cyclohexyl), 1.30 (3H, t, J = 7, $CO_2CH_2CH_3$); δ_C (125 MHz; $CDCl_3$) 176.1, 172.1 (NH*C*O, *C*O_2Et), 60.8 (NH*C*), 60.6 (CO_2CH_2), 41.6 (*C*HCH_2CO_2), 37.0 (cyclohexyl *C*H_2), 36.3, 34.6 (*C*H_2CO_2, NHCO*C*H_2), 32.3, 25.3, 23.0, 22.0 (cyclohexyl *C*H_2), 14.1 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 240 (M + H^+, 100%), 224 (9), 196 (16), 166 (10), 122 (6) (Found: M + H^+, 240.1559. $C_{13}H_{21}NO_3$ requires for M + H^+, 240.1560).

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