Tandem radical cyclisation of enamides mediated by tin hydride; pyrrolizidinone or indolizidinone ring formation

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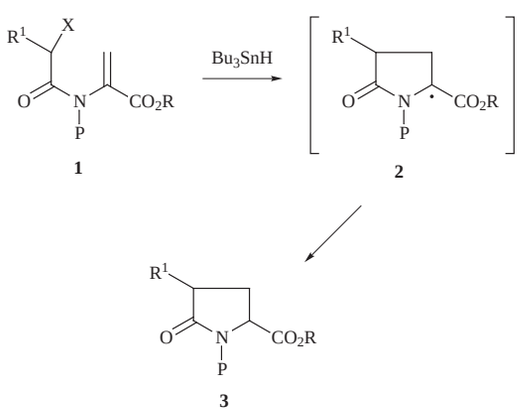
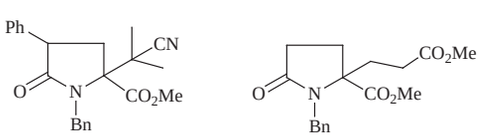
The tin hydride-mediated cyclisation of a variety of enamides under mild, neutral reaction conditions has been investigated. Enamides derived from pyruvate were reacted with R_3SnH–AIBN to generate α-carbamoylmethyl radicals which underwent 5-*endo* cyclisation to give cyclic α-amino ester radicals. Subsequent 6-*endo* or 5-*exo* cyclisation was observed leading to the formation of indolizidinone and pyrrolizidinone products respectively. The reaction pathway was governed by the alkene substitution. If an electron-rich double bond was used the cyclisation was under thermodynamic control and a 6-membered ring was observed. Five-membered rings were formed on reaction of the α-amino ester radical with unsaturated esters or ketones. The ester or ketone functional group can stabilise the radical produced on 5-*exo* cyclisation and pyrrolizidinones could be prepared in up to 66% yield. Stannane by-products were also isolated from some reactions. These were thought to be derived from a competitive Michael-type addition of the tin radical to the enamide double bond.

The preparation of saturated 5- and 6-membered nitrogen heterocycles has attracted the attention of synthetic chemists for many years. Their widespread occurrence and diverse range of important biological activities make them attractive targets. One important method for constructing the heterocyclic ring is *via* a radical cyclisation reaction which is most commonly accomplished using tin hydrides.[1] By far the most common strategy involves cyclisation of unsaturated halide (or related) precursors in a "favoured" 5- or 6-*exo* manner.[2] A wide variety of substituted N-heterocycles can be accessed, often in excellent yields, using this approach. We became interested in extending the range of N-heterocycles which can be prepared (using free-radical methods) still further by investigating alternative and less popular modes of cyclisation. This included 5-*endo* cyclisation reactions and in particular the cyclisation of α-carbamoylmethyl radicals to form substituted pyrrolidinones. Ikeda and co-workers[3] were the first to demonstrate that this type of radical, prepared from reaction of halo-enamides with Bu_3SnH, could undergo this unusual "disfavoured" mode of cyclisation. The presence of the enamide carbonyl was shown to be crucial; similar enamines underwent simple reduction. A range of mono- and bicyclic-pyrrolidinones have since been prepared using this method[4] and alternative radical generating agents [namely Ni[5] and $Mn(OAc)_3$[6]] have been used to effect this transformation. We have shown that this mode of cyclisation can be extended to the preparation of substituted pyroglutamates **3**, starting from enamides **1** (Scheme 1).[7] These reactions can proceed in excellent yield and the lactams produced may, for example, be elaborated to biologically important glutamic acid derivatives.[8] The preparation of enantiomerically enriched/pure products has also been explored using chiral ester auxiliaries (*e.g.* R = menthyl or 8-phenylmenthyl, Scheme 1).[9] Recently, we have investigated the mechanism of these cyclisations and shown that they proceed *via* α-amino ester radicals **2**.[8] These can be coupled to other radicals [*e.g.* radicals produced on decomposition of AIBN or 1,1′-azobis(cyclohexanecarbonitrile) (ACN)] or trapped by electron-poor alkenes (such as methyl methacrylate) to give α-substituted pyroglutamates including **4** and **5**. Encouraged by the intermolecular



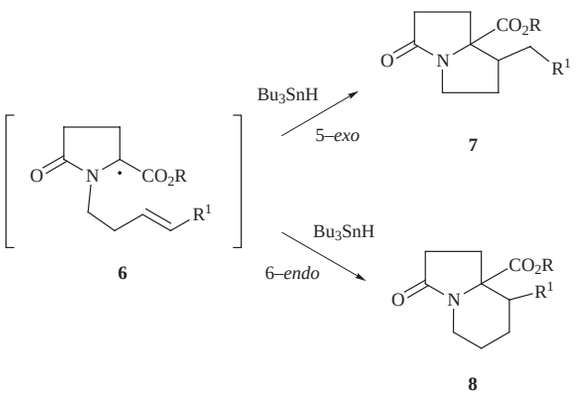
Scheme 1



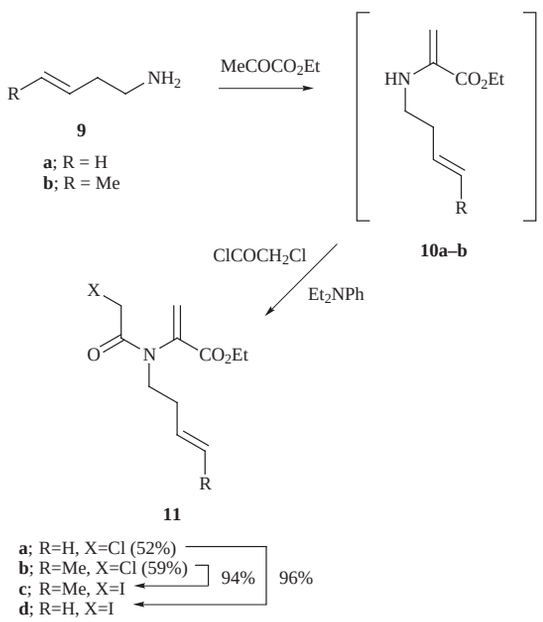
trapping of these radicals, we decided to explore (entropically favoured) intramolecular trapping so as to produce bicyclic N-heterocycles in a one-pot reaction. Hence cyclisation of radicals of type **6** could proceed in a 5-*exo* or 6-*endo* manner to give pyrrolizidinones **7** or indolizidinones **8** respectively (Scheme 2).[10] These bicyclic lactams are useful precursors to biologically important pyrrolizidine or indolizidine alkaloids.[11]

Results and discussion

Initial work centred on the preparation of dienes **11a**–**d** starting from unsaturated amines **9a**–**b** (Scheme 3). The amines, prepared on reduction ($LiAlH_4$–$AlCl_3$) of the corresponding nitriles, were reacted with ethyl pyruvate and the resultant



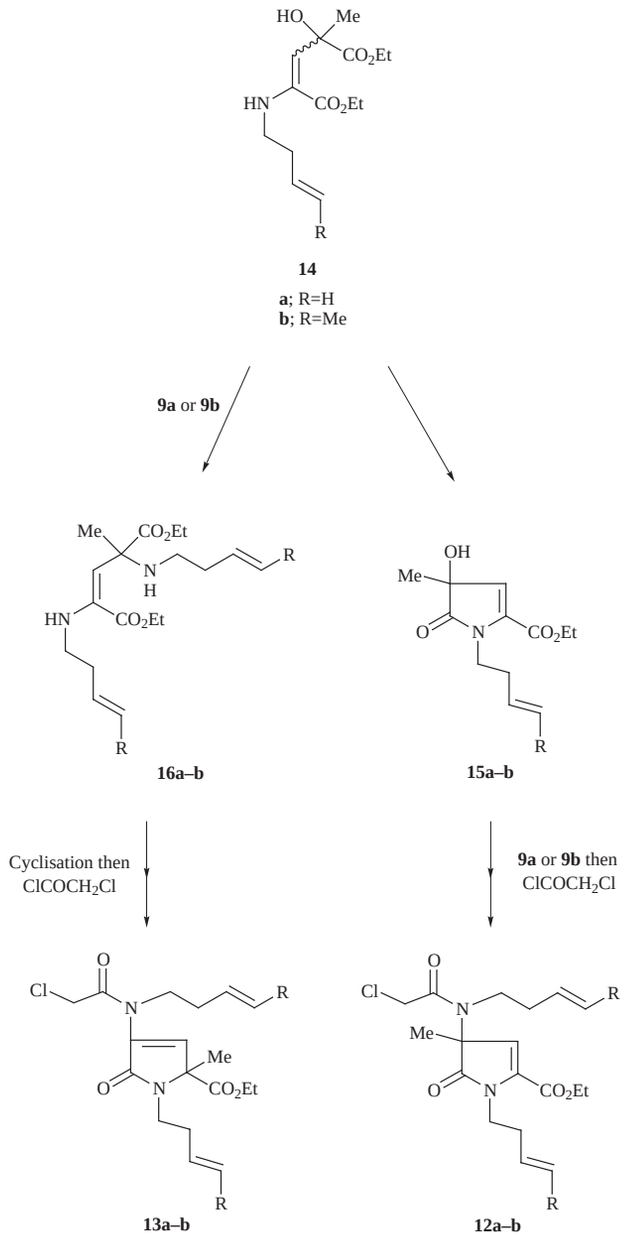
Scheme 2



Scheme 3

(imine or) enamine **10a**–**b** was immediately N-acylated using chloroacetyl chloride and diethyl aniline.[12] After considerable optimisation, this one-pot method was found to give chlorides **11a**–**b** in >50% yield. The reaction conditions were found to be crucial; competitive or even exclusive formation of a pyrrolidenone (in 17–44% yield) was observed in some cases (Scheme 4). The two possible pyrrolidenone by-products, namely **12a**–**b** and **13a**–**b**, could be formed by nucleophilic addition of enamine **10a**–**b** to ethyl pyruvate giving *E*- and/or *Z*-enamines **14a**–**b**. Cyclisation of the *Z*-isomer of **14a**–**b** to pyrrolidenone **15a**–**b** followed by nucleophilic substitution of the allylic alcohol (by amine **9a**–**b**) and acylation would give **12a**–**b**. A similar pathway to **13a**–**b**, starting from the *E*-isomer of **14a**–**b**, which involves the formation, cyclisation and acylation of **16a**–**b** can also be proposed. Only one pyrrolidenone isomer was isolated from these reactions. Using $^{3}J_{HC}$ correlations observed in a gHMBC (gradient heteronuclear multiple bond correlation) NMR experiment, it was possible to determine that **13b**, rather than **12b**, was produced on reaction of **9b**. The formation of the pyrrolidenone could be minimised, and the desired halides **11a**–**b** maximised, by slow addition (1 h) of 1 equiv. of the pyruvate to 1 equiv. of the amine **9a**–**b** in boiling benzene (0.09 M).† The resultant chlorides **11a**–**b** could then be converted to the

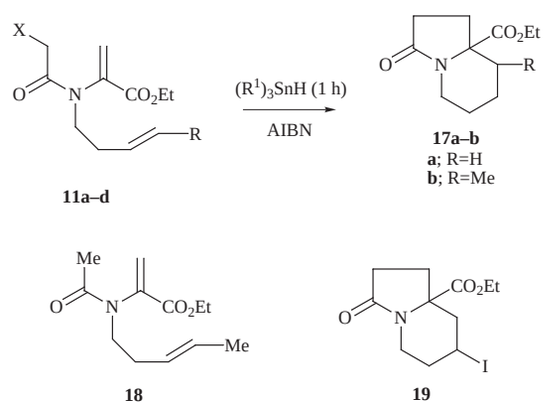
† Immediate addition of ethyl pyruvate (1 equiv.) to amine **9b** (1 equiv.) in boiling benzene (0.27 M) followed by heating overnight and reaction with chloroacetyl chloride gave **13b** in 44% yield and **11b** in only 5% yield.



Scheme 4

corresponding iodides **11c**–**d** by reaction with sodium iodide (Scheme 3).

Treatment of halides **11a**–**c** with 1.1 equiv. of Bu_3SnH or Ph_3SnH gave rise to the indolizidinones **17a**–**b** in 21–40% yield (Scheme 5, Table 1). These were formed from a 5-*endo*–6-*endo* cyclisation sequence and no pyrrolizidinones were isolated



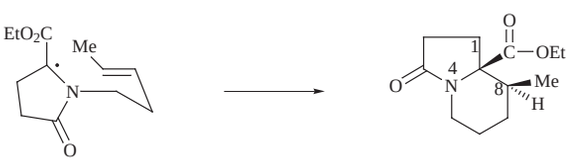
Scheme 5

Table 1 Tin hydride mediated cyclisations of **11a–d**

Entry	Halide **11**	X	R	R^1	Solvent	Products (yield, %)
1	**a**	Cl	H	Bu	Benzene	**17a** (21[a])
2	**b**	Cl	Me	Bu	Toluene	**17b** (25/27[a])
3	**b**	Cl	Me	Ph	Toluene	**17b** (40)
4	**c**	I	Me	Bu	Toluene	**17b** (38) + **18** (21)
5	**c**	I	Me	Ph	Toluene	**17b** (40) + **18** (13)
6	**d**	I	H	Bu	Benzene	**19** (15[a])

[a] Bu_3SnH added over 5 rather than 1 h.

although some simple reduction, to give acetamide **18**, was observed starting from iodide **11c** (entries 4 and 5). Generally higher yields were obtained when using Ph_3SnH and the Ph_3SnX by-products were more easily removed from **17b** (on aqueous KF workup and column chromatography) than the corresponding Bu_3SnX compounds. The exclusive 6-*endo* cyclisation of the intermediate α-amido ester radical is noteworthy. Related radicals are known to undergo 6-*endo* cyclisation but this is often accompanied by competitive 5-*exo* cyclisation.[13] The preference for the 6-membered ring may result from the stability of the (captodative) α-amino ester radical which leads to reversible ring closure and formation of the thermodynamically favoured product.[14] This readily explains the formation of **17a** where 5-*exo* cyclisation would give a primary radical while the observed 6-*endo* reaction proceeds *via* a more stable secondary radical. However, the deciding factor for **17a** and **17b** could be the formation of a less strained 5,6- rather than 5,5-ring system. Molecular modelling calculations using CHARMm v22 or MSI Cerius[2] v3.8 were consistent with the 5,6-ring system being (*ca.* 14–21 kcal mol^{-1}) lower in energy than the 5,5-ring system. These models possessed similar bond angles to those reported[15] from X-ray analysis of related pyrrolizidinones. Only one diastereomer of **17b** was isolated and this was tentatively assigned, from NMR experiments, the stereochemistry shown in Scheme 6. Overlap in the NMR spectra

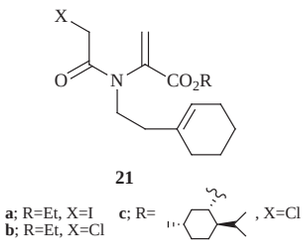


20 **17b**

Scheme 6

prevented unambiguous assignment but ^1H–^1H NOEs and $^3J_{HH}$, $^3J_{HC}$ coupling constants were consistent with the stereochemistry shown. For example, the long range coupling for the hydrogen on C-8 and the ester carbonyl carbon was in the range $J = 6$–8 Hz; this is good evidence for a dihedral angle approaching 180° in which both atoms are axial. The formation of this stereoisomer is also consistent with a chair (piperidine) transition state **20** in which the methyl substituent adopts the energetically favoured pseudo-equatorial (rather than axial) position. Reaction of iodide **11d** with Bu_3SnH unexpectedly gave rise to the secondary iodide **19**, rather than **17b**, albeit in low yield (Table 1, entry 6). This was the only product which could be isolated/characterised from this reaction and **19** is most likely formed *via* iodine atom transfer which is surprising because of the reaction conditions used (*i.e.* high dilution and use of 1.1 equiv. of Bu_3SnH). The NMR spectra suggested the formation of one isomer of **19** (the stereochemistry of which was not deduced) and attempts to improve the yield (*e.g.* by using <1 equiv. of Bu_3SnH) were unsuccessful.

Cyclisation of the *N*-2-(cyclohex-1-enyl)ethyl derivative **21a** was then investigated. Reaction with Ph_3SnH (added over 5 h) in boiling benzene produced the tricycle **22** as one diastereomer



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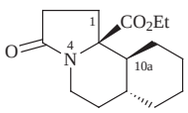
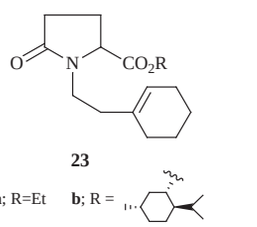


22

a; R=Et, X=I **c**; R= , X=Cl
b; R=Et, X=Cl



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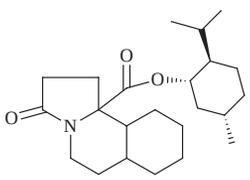


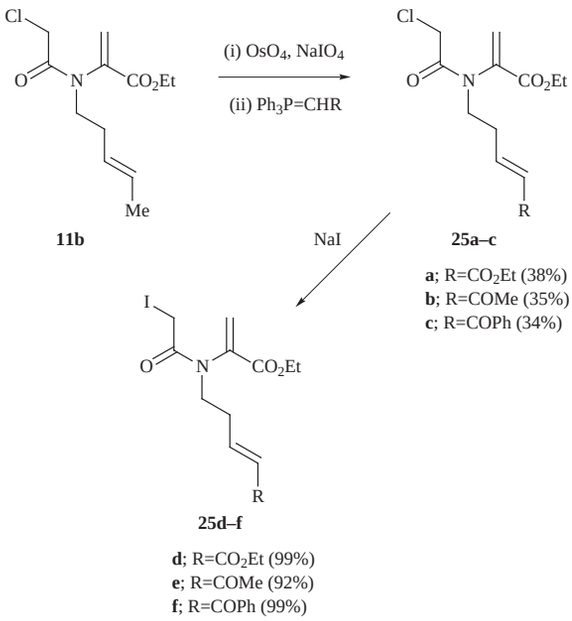
24

a; R=Et **b**; R =

(from the NMR spectra) in 61% yield and the pyrrolidinone **23a** (derived from reaction of the intermediate α-amino ester radical with Ph_3SnH) in 26% yield. Exclusive 5-*endo*–6-*endo* tandem cyclisation is consistent with the reactions of **17a–d** and for **21a** 5-*exo* cyclisation would have to involve attack at a sterically hindered trisubstituted double bond. Similar results‡ were obtained on reaction of the corresponding chloride **21b** with Bu_3SnH or Ph_3SnH, added over 1, 5 or 12 h using benzene or EtOAc as the solvent. In some cases, the use of Bu_3SnH did lead to the formation of a second minor diastereomer of **22**. Thus reaction of iodide **21a** with Bu_3SnH (added over 5 h) in boiling benzene gave **22** in 62% yield as a 6:1 mixture of isomers (and **23a** in 21% yield). The predominant or exclusive diastereomer of **22** isolated from these reactions was tentatively assigned the stereochemistry shown based on NMR experiments. Overlap in the NMR spectra prevented unambiguous assignment but a long range coupling between the C-10a hydrogen and the ester carbonyl carbon (in the range 6–8 Hz) was consistent with a dihedral angle of 180°. The cyclisation of menthyl ester derivative **21c** was also investigated. Precursors of this type, which contain a chiral ester auxiliary, could allow the preparation of enantiomerically pure cyclic products.[9] However reaction of **21c** with Bu_3SnH (added over 5 h) in boiling benzene gave **24** in 38% yield and GC-MS showed the formation of 6 diastereomers (observed as 3 pairs, in the ratio 23.5:30.3:9.3:2.3:1.0:1.2). Pyrrolidinone **23b** was also isolated (as a 2.4:1 mixture of isomers) in 25% yield. Similar yields and isomer ratios were obtained when using Ph_3SnH. Carrying out the Bu_3SnH reaction in toluene gave similar results while reaction at lower temperature, in boiling EtOAc, gave **24** in lower yield (20%) as a mixture of 5 diastereoisomers (35.6:43.5:1.5:2.2:1). All these reactions gave two major diastereomers which were formed in a similar ratio (1:1.2–1.4). These preliminary results suggest that this method is unlikely to give good stereocontrol and hence the use of alternative ester auxiliaries was not explored.

The tandem reactions described up to now have involved cyclisation of the intermediate α-amido ester radical on to an electron-rich double bond. We envisaged that precursors bearing an electron-poor alkene could be prepared from **11b** (Scheme 7). Selective oxidative cleavage of the most electron-rich double bond was expected to give an aldehyde which on Wittig reaction (with various phosphoranes) would allow the preparation of dienes **25a–c**. Although O_3 (followed by dimethyl sulfide) was found to react with both alkenes of **11b**,

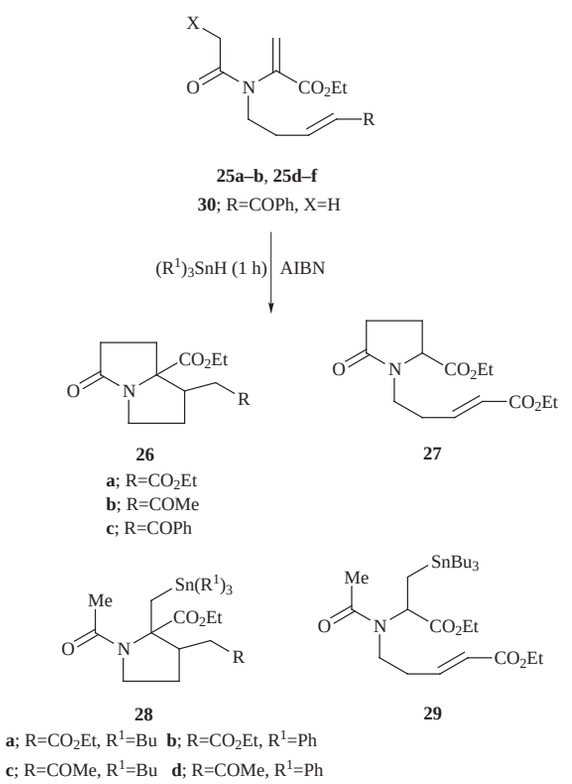
‡ Under these conditions, **22** and **23a** were formed in 41–69 and 5–21% yield respectively.



Scheme 7

even after short reaction times, treatment with OsO_4–$NaIO_4$ selectively cleaved the desired C=C bond to give the aldehyde. This aldehyde was immediately reacted with stabilised phosphoranes to afford the desired *trans*-alkene isomers **25a**–**c** in modest yields. The low yields for these reactions were thought to result from a competitive Michael addition of the phosphorane to the enamide double bond. This was supported by reaction of **11b** with $Ph_3P{=}CHCO_2Et$; after stirring overnight in CH_2Cl_2 TLC showed the disappearance of the starting material and the two characteristic alkene singlets (of the enamide double bond) were no longer present in the crude ^1H NMR spectrum. The primary chlorides **25a**–**c** could then be easily converted to the corresponding iodides **25d**–**f** in good yield.

The reaction of dienes **25a**–**b** and **25d**–**f** with Bu_3SnH or Ph_3SnH is shown in Scheme 8 and Table 2. Changing to an



Scheme 8

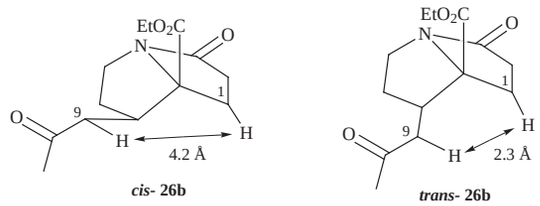


Fig. 1

electron-poor double bond acceptor was found to have a dramatic effect on the reaction and no products resulting from a 5-*endo*–6-*endo* tandem cyclisation were observed. Thus reaction of **25a** with Bu_3SnH or Ph_3SnH gave the pyrrolizidinone **26a** (derived from a 5-*endo*–5-*exo* cyclisation) the pyrrolidinone **27** and the tin adduct **28a** (Table 2, entries 1 and 2). The formation of **28a** can be explained by a Michael-type addition of the tin radical to **25a** followed by 5-*exo* cyclisation on to the acrylate double bond and subsequent reduction of the C–Cl bond using a further equivalent of tin hydride. The reverse is also possible whereby C–Cl bond cleavage precedes tin addition but this is thought to be more likely for iodide precursors (see later). This was the only reaction observed on treatment of chloride **25b** with Ph_3SnH or Bu_3SnH (entries 3 and 4). The use of iodide **25d** was found to improve the yield of **26a** and a mixed EtOAc–toluene solvent was used because of the poor solubility of the precursor in toluene (entries 5 and 6). The change in reaction pathway was most pronounced for iodide **25e**. Whereas chloride **25b** gave no tandem cyclisation, the corresponding iodide **25e** underwent 5-*endo*–5-*exo* cyclisation to give an excellent yield of the pyrrolizidinone **26b** (entries 7 and 8). A similar result was observed on reaction of the related iodide **25f** to give **26c** (entries 9–11). The pyrrolizidinones **26a**–**c** were formed as a mixture of diastereomers and the stereochemistry of the isomers of **26b** could be deduced from observed NOE interactions between the hydrogens attached to atoms on C-1 and C-9 (Fig. 1). A strong NOE interaction was observed for the minor isomer whereas no such interaction was observed for the major isomer. Energy minimised molecular models (MSI Cerius^2 v3.8) of the compounds suggest that the distance between the hydrogen atoms is greater for the *cis*-isomer§ (*ca.* 4.2 Å) than for the *trans*-isomer (*ca.* 2.3 Å). This established that the major isomer of **26b** was *cis* and the major isomers of **26a** and **26c** were also assigned as *cis* based on a comparison of the ^1H NMR spectra. A characteristic feature of these spectra were the chemical shifts of the peaks for the two C-5 hydrogens. These were observed at *ca.* δ 3.6 and 3.3 ppm for the *cis*-isomers while for the *trans*-isomers they were more separated (at *ca.* δ 3.75 and 3.1 ppm). The formation of pyrrolizidinones rather than indolizidines can be explained by the introduction of a radical stabilising group on the acceptor double bond. The ester or ketone functional group can stabilise the radical formed on 5-*exo* cyclisation. As a result the reaction is not reversible and the kinetic product, namely the 5-membered ring, is formed.

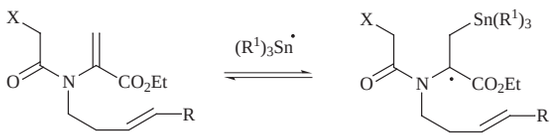
The formation of tin adducts **28a**–**d** and **29** shows that the tin radical can add to the dehydroamino ester double bond. This is expected to be a *reversible* process and if cyclisation of radical **31** is slow then β-elimination of the tin radical can regenerate the starting material (Scheme 9). This is what we observed for precursors bearing an electron-rich double bond acceptor (R = Me). Introduction of an electron withdrawing group (*e.g.* R = COMe) leads to a fast and irreversible 5-*exo* cyclisation of **31** which competes very effectively with β-elimination. The extent of tin addition to the double bond depends on the nature of the leaving group X. Tin adducts were generally formed in higher yields when chlorides rather than iodides were used and the stronger C–Cl bond is expected to lead to slower α-carb-

§ The *cis*-isomer is defined as the isomer in which the ethyl ester and ketone side chains are *cis* to one another.

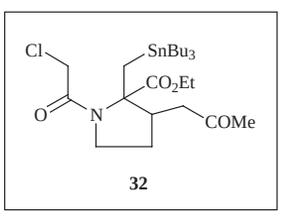
Table 2 Tin hydride mediated cyclisations of **25a**–**b** and **25d**–**f**

Entry	**25**	X	R	R^1	Solvent[a]	Products (yield, %)	**26** *cis*-:*trans*-
1	**a**	Cl	CO_2Et	Bu	Toluene	**26a** (19) + **27** (11) + **28a** (19)	2.6:1
2	**a**	Cl	CO_2Et	Ph	Toluene	**26a** (18) + **27** (8) + **28b** (22)	2.7:1
3	**b**	Cl	COMe	Bu	Toluene	**28c** (37)	—
4	**b**	Cl	COMe	Ph	Toluene	**28d** (47)	—
5	**d**	I	CO_2Et	Bu	Toluene–EtOAc	**26a** (40) + **28a** (3) + **29** (11)	2.3:1
6	**d**	I	CO_2Et	Ph	Toluene–EtOAc	**26a** (30) + **28b** (35)	2.8:1
7	**e**	I	COMe	Bu	Toluene–EtOAc	**26b** (65)	2.6:1
8	**e**	I	COMe	Ph	Toluene–EtOAc	**26b** (66)	2.6:1
9	**f**	I	COPh	Bu	Toluene–EtOAc	**26c** (55)	1.7:1[b]
10	**f**	I	COPh	Ph	Toluene–EtOAc	**26c** (52)	1.6:1[b]
11	**f**	I	COPh	Ph	EtOAc	**26c** (57) + **30** (8)	1.8:1[b]

[a] When using a mixed solvent system the ratio of toluene : EtOAc was *ca.* 10 : 1. [b] Ratio determined from the ^{1}H NMR spectrum.



25a–b, 25d–f **31**



32

Scheme 9

amoylmethyl radical generation. As a result the tin radical is likely to add to the double bond of **25** before abstracting a chlorine atom. This is supported by the isolation (on one occasion) of the chloro-stannane **32** produced (in 9% yield) from reaction of **25b** with Bu_3SnH. With iodide precursors the tin radical is more likely to cleave the weak C–I bond first and thus no iodo-stannane derivatives were recovered.

This work has demonstrated two different tandem cyclisations of enamides. The free-radical method has been shown to provide a quick and mild entry to various pyrrolizidinones or indolizidinones. This flexible approach should find application in the preparation of medicinally important pyrrolizidine and indolizidine alkaloids. Further studies in this area are currently underway.

Experimental

IR spectra were recorded on an ATI Mattison Genesis FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 270 or a Bruker DRX500 spectrometer equipped with a Bruker triple-resonance probe and *z*-axis gradient system at 300 K. The spectra were assigned using DEPT, gCOSY, gHSQC and gHMBC experiments. Coupling constants (*J*) were recorded in hertz to the nearest 0.5 Hz. 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/100 cm^3. Gas chromatography was performed on a Philips Pye Unicam PU4500 (column SE54, 30 m × 0.25 mm, He 40 psi) fitted with a flame ionisation detector. Samples were injected at 200 °C and after 2 min the temperature was increased by 8 °C min^{-1} to 300 °C. 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 microns). Solvents were purified/dried using standard literature methods. Petroleum ether refers to the fraction with bp 40–60 °C. Bu_3SnH and Ph_3SnH were purchased from Lancaster Synthesis Ltd. Elemental analyses were performed by the Chemical Analytical Services Unit, University of Newcastle.

General procedure for the formation of halide precursors 11a–b and 21b–c

To a stirred (0.08–0.10 M) solution of the amine (7.48–15.97 mmol) in benzene (75–185 cm^3), was added ethyl or (1*S*,3*S*,4*R*)-menthyl pyruvate[16] (6.73–15.97 mmol) either immediately or *via* a syringe pump (1 h) while the solution was stirred under Dean–Stark conditions for 2 h. The solution was then cooled to 0 °C and magnesium sulfate (8.23–17.57 mmol) was added. Chloroacetyl chloride (7.48–15.97 mmol) followed by *N*,*N*-diethylaniline (7.48–15.97 mmol) were then added. After 5 h the solution was filtered and the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether (20–50 cm^3), washed with water, 1 M aqueous hydrochloric acid, brine, dried (magnesium sulfate) and the solvent evaporated *in vacuo*. Column chromatography (silica) afforded **11a**–**b** or **21b**–**c** as oils (48–63%).

Ethyl 2-[*N*-(but-3-enyl)-2-chloroethanamido]propenoate 11a. (Found: C, 54.0; H, 6.8; N, 5.3. $C_{11}H_{16}ClNO_3$ requires C, 53.8; H, 6.6; N, 5.7%); R_f 0.2 (petroleum ether–diethyl ether, 2:1); ν_{max} (thin film) 2984 (m), 1729 (s), 1636 (m), 1308 (m), 1236 (m), 1193 (m), 1138 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.59 (1H, s, NC=C*H*), 5.96 (1H, s, NC=C*H*), 5.83–5.68 (1H, m, C*H*=CH_2), 5.15–5.03 (2H, m, CH=CH_2), 4.29 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.01 (2H, s, CH_2Cl), 3.69–3.51 (2H, m, NCH_2), 2.35–2.28 (2H, m, NCH_2CH_2), 1.33 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 169.8, 162.9 (N*C*O and *C*$O_2CH_2CH_3$), 137.5 (N*C*$CO_2CH_2CH_3$), 134.3 (*C*H=CH_2), 129.0 (CH=*C*H_2), 117.2 (NC=*C*H_2), 62.1 ($CO_2CH_2CH_3$), 47.1 (NCH_2), 40.4 (CH_2Cl), 31.2 (NCH_2CH_2), 13.6 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 263 (M^{35} + NH_4^+, 10%), 246 (M^{35} + H^+, 100), 212 (25), 200 (10), 184 (5), 170 (35), 138 (20), 128 (15), 96 (5) (Found: M^{35} + H^+, 246.0892. $C_{11}H_{16}ClNO_3$ requires for M^{35} + H^+, 246.0897).

Ethyl (*E*)-2-[*N*-(pent-3-enyl)-2-chloroethanamido]propenoate 11b. R_f 0.25 (petroleum ether–diethyl ether, 2:1); ν_{max} (thin film) 2928 (w), 1724 (s), 1659 (m), 1631 (s), 1265 (s), 738 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.59 (1H, s, NC=C*H*), 5.97 (1H, s, NC=C*H*), 5.48–5.32 (2H, m, C*H*=C*H*CH_3), 4.29 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.02 (2H, s, CH_2Cl), 3.62–3.44 (2H, m, NCH_2), 2.28–2.19 (2H, m, NCH_2CH_2), 1.64 (3H, d, *J* 6.5, $CHCH_3$), 1.33 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 166.3, 162.7 (N*C*O and *C*$O_2CH_2CH_3$), 137.5 (N*C*$CO_2CH_2CH_3$), 127.7 (NC=*C*H_2), 127.1, 126.5 (*C*H=*C*HCH_3), 61.4 ($CO_2CH_2CH_3$), 47.5 (NCH_2), 40.4 (CH_2Cl), 29.9 (NCH_2CH_2), 17.3 (CH_3), 13.5 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 277 (M^{35} + NH_4^+, 5%), 260

(M^{35} + H^+, 100), 226 (10), 184 (5), 128 (10) (Found: M^{35} + H^+, 260.1056. $C_{12}H_{18}ClNO_3$ requires for M^{35} + H^+, 260.1053).

Ethyl 2-[*N*-(2-cyclohex-1-enylethyl)-2-chloroethanamido]-propenoate 21b. R_f 0.3 (petroleum ether–diethyl ether, 2:1); ν_{max} (thin film) 2930 (s), 1727 (s), 1670 (s), 1448 (w), 1310 (w), 1232 (m), 1160 (m), 735 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.55 (1H, s, NC=C*H*), 5.93 (1H, s, NC=C*H*), 5.35 (1H, br s, C=C*H*CH_2), 4.28 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.98 (2H, s, CH_2Cl), 3.58–3.45 (2H, m, NCH_2), 2.19–2.14 (2H, m, NCH_2CH_2), 2.01–1.86 (4H, m, CH_2C=CHCH_2), 1.64–1.48 (4H, m, C=CH$CH_2CH_2CH_2$), 1.33 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 165.4, 162.8 (NCO and $CO_2CH_2CH_3$), 137.9 ($NCCO_2CH_2CH_3$), 133.8 (C=CHCH_2), 128.0 (C=CH_2), 122.8 (C=CHCH_2), 61.6 ($CO_2CH_2CH_3$), 46.1 (NCH_2), 40.8 (CH_2Cl), 35.5 (NCH_2CH_2), 27.7 (CH_2C=CH), 24.7 (C=CHCH_2), 22.1, 21.8 (C=CH$CH_2CH_2CH_2$), 13.6 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 300 (M^{35} + H^+, 100%) (Found: M^{35} + H^+, 300.1366. $C_{15}H_{22}ClNO_3$ requires for M^{35} + H^+, 300.1366).

(1*S*,3*S*,4*R*)-3-Menthyl 2-[*N*-(2-cyclohex-1-enylethyl)-2-chloroethanamido]propenoate 21c. R_f 0.45 (petroleum ether–diethyl ether, 2:1); a_D^{20} +38.1 (*c* = 0.8, EtOH); ν_{max} (thin film) 2937 (s), 2871 (m), 1723 (s), 1671 (s), 1449 (w), 1405 (w), 1262 (m), 1182 (w), 738 (s) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.53 (1H, s, NC=C*H*), 5.88 (1H, s, NC=C*H*), 5.45 (1H, apparent br s, C=C*H*), 4.82 (1H, dt, *J* 4.5 and 10.5, CO_2CH), 3.97 (2H, s, CH_2Cl), 3.58 (1H, apparent br s, NC*H*), 2.18 (1H, apparent br s, NC*H*), 2.05–0.95 (19H, m, NCH_2CH_2, CH_2CH_2C=CHCH_2CH_2, $CO_2CHCH_2CHCH_2CH_2CH_2$ and $CHCH(CH_3)_2$), 0.93 (3H, d, *J* 7, CH_3CHCH_3), 0.91 (3H, d, *J* 7, CH_3CHCH_3), 0.79 (3H, d, *J* 7, $CHCH_3$); δ_C (67.5 MHz, $CDCl_3$) 165.6, 162.7 (NCO and CO_2CH), 138.5 (C=CH), 134.0 (NC=CH_2), 127.8 (NC=CH_2), 123.0 (C=CH), 76.2 (CO_2CH), 46.8 ($CHCH(CH_3)_2$), 46.4 (NCH_2), 41.2 (CO_2CHCH_2), 40.4 (CH_2Cl), 35.4 (NCH_2CH_2), 33.9 (CH_2C=CH), 31.2 ($CH(CH_3)_2$), 28.0 (C=CHCH_2), 26.3 ($CHCH_3$), 25.0, 23.1, 22.6, 22.5 ($CO_2CHCHCH_2CH_2$ and C=CH$CH_2CH_2CH_2$), 22.1, 20.5 ($CH(CH_3)_2$), 16.0 ($CHCH_3$); *m*/*z* (CI, NH_3) 410 (M^{35} + H^+, 100%), 376 (30) (Found: M^{35} + H^+, 410.2457. $C_{23}H_{36}ClNO_3$ requires for M^{35} + H^+, 410.2462).

Ethyl 4-[*N*-(chloroethanoyl)-*N*-(pent-3-enyl)amino]-2-methyl-*N*-(pent-3-enyl)-5-oxo-3,4-didehydropyrrolidine-2-carboxylate 13b. To a stirred (0.28 M) solution of amine **9b** (2.34 g, 27.54 mmol) in benzene (100 cm^3) was added ethyl pyruvate (3.20 g, 3.05 cm^3, 27.54 mmol) in one portion and the solution was stirred under Dean–Stark conditions for 12 h. The solution was then cooled to 0 °C and magnesium sulfate (3.65 g, 30.29 mmol) was added. Chloroacetyl chloride (3.11 g, 2.20 cm^3, 27.54 mmol) followed by *N*,*N*-diethylaniline (4.11 g, 4.39 cm^3, 27.54 mmol) were then added. After 5 h the solution was filtered and the solvent removed *in vacuo*. The residue was dissolved in diethyl ether (20–50 cm^3), washed with water, 1 M aqueous hydrochloric acid, brine, dried (magnesium sulfate) and the solvent was evaporated. Column chromatography (petroleum ether–diethyl ether, 2:1) afforded **13b** (2.40 g, 44%) and **11b** (357 mg, 5%) as oils.

13b. R_f 0.17 (petroleum ether–diethyl ether, 2:1); ν_{max} (thin film) 2936 (w), 1696 (s), 1445 (w), 1394 (w), 1248 (m), 1114 (w), 737 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.89 (1H, s, NC=C*H*), 5.60–5.26 (4H, m, 2 × C*H*=C*H*CH_3), 4.20 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.04 (2H, s, CH_2Cl), 3.84–3.55 (2H, m, NCH_2), 3.54–3.18 (2H, m, NCH_2), 2.37–2.28 (2H, m, NCH_2CH_2), 2.26–2.19 (2H, m, NCH_2CH_2), 1.69–1.56 (9H, m, 2 × $CHCH_3$ and CCH_3), 1.28 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 168.6, 166.0, 165.8 (2 × NCO and $CO_2CH_2CH_3$), 139.3 (NC=CH), 137.2 (NC=CH), 127.6, 127.4, 126.9, 126.6 (2 × CH=$CHCH_3$), 66.9 ($NC(CH_3)CO_2CH_2CH_3$), 62.7 ($CO_2CH_2CH_3$), 47.5 (CH_2Cl), 41.4, 41.2 (2 × NCH_2), 31.2, 31.0 (2 × NCH_2CH_2), 19.4 ($NCCH_3$), 17.5 (2 × CH=CHCH_3), 13.6 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 397 (M^{35} + H^+, 100%), 363 (20) (Found: M^{35} + H^+, 397.1890. $C_{20}H_{29}ClN_2O_4$ requires for M^{35} + H^+, 397.1889).

General procedure for the preparation of alkenes 25a–c

To a solution of **11b** (1–5 mmol) and osmium tetroxide (1 crystal) in dioxane–water (2:1, 10–50 cm^3) was added sodium periodate (2.2–11 mmol) dropwise over 0.3 h. After stirring for 2 h, the solution was extracted using ethyl acetate (3 × 20 cm^3) and the combined organic extracts were washed with water (20–50 cm^3). The organic layer was dried ($MgSO_4$) and evaporated to afford crude aldehyde to which dichloromethane (10–50 cm^3) was immediately added. The phosphorane (1.1–5.5 mmol) was then added portionwise, the mixture stirred for 4 h and further dichloromethane (20 cm^3) added. After washing with water (10–30 cm^3), the solution was evaporated and purified using column chromatography (silica) to afford **25a–c** (34–38%) as oils.

Ethyl (*E*)-2-[*N*-(4-ethoxycarbonylbut-3-enyl)-2-chloroethanamido]propenoate 25a. R_f 0.4 (diethyl ether); ν_{max} (thin film) 2982 (s), 2940 (m), 1776 (m), 1722 (s), 1676 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.88 (1H, dt, *J* 16 and 7, C*H*=CHCO_2), 6.47 (1H, br s, NC=C*H*), 5.94 (1H, br s, NC=C*H*), 5.86 (1H, d, *J* 16, CH=C*H*CO_2), 4.29 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.17 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.97 (2H, br s, $COCH_2Cl$), 3.65 (2H, t, *J* 6.5, NCH_2), 2.49 (2H, dt, *J* 7 and 6.5, NCH_2CH_2), 1.34 (3H, t, *J* 7, $CO_2CH_2CH_3$), 1.27 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 166.0, 165.9, 163.0 (NCO and 2 × $CO_2CH_2CH_3$), 144.3 (CH=$CHCO_2CH_2CH_3$), 138.2 (NC=CH_2), 128.3 (NC=CH_2), 123.3 (CH=$CHCO_2$), 62.1, 60.1 (2 × $CO_2CH_2CH_3$), 46.8 (NCH_2), 41.1 (CH_2Cl), 30.0 (NCH_2CH_2), 14.1, 14.0 (2 × $CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 337 (M^{37} + NH_4^+, 33%), 335 (M^{35} + NH_4^+, 100), 320 (M^{37} + H^+, 10), 318 (M^{35} + H^+, 22), 279 (30) (Found: M^{35} + NH_4^+, 335.1360. $C_{14}H_{20}ClNO_5$ requires for M^{35} + NH_4^+, 335.1374).

Ethyl (*E*)-2-[*N*-(5-oxohex-3-enyl)-2-chloroethanamido]propenoate 25b. R_f 0.2 (diethyl ether); ν_{max} (thin film) 2954 (s), 1725 (m), 1674 (w), 1264 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.75 (1H, dt, *J* 16 and 7, C*H*=CHCO), 6.59 (1H, br s, NC=C*H*), 6.09 (1H, d, *J* 16, CH=CHCO), 5.93 (1H, br s, NC=CH), 4.30 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.97 (2H, br s, $COCH_2Cl$), 3.70 (2H, t, *J* 6, NCH_2), 2.51 (2H, dt, *J* 7 and 6, NCH_2CH_2), 2.25 (3H, s, $COCH_3$), 1.35 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 198.1 ($COCH_3$), 166.1, 162.9 (NCO and CO_2Et), 143.7 (CH=CHCO), 132.8 (CH=CHCO), 138.0 (NC=CH_2), 128.6 (NC=CH_2), 62.2 ($CO_2CH_2CH_3$), 46.5 (NCH_2), 41.1 (CH_2Cl), 30.5 (NCH_2CH_2), 26.6 ($COCH_3$), 13.9 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 307 (M^{37} + NH_4^+, 36%), 305 (M^{35} + NH_4^+, 100), 290 (M^{37} + H^+, 23), 288 (M^{35} + H^+, 60), 254 (23) (Found: M^{35} + NH_4^+, 305.1267. $C_{13}H_{18}ClNO_4$ requires for M^{35} + NH_4^+, 305.1268).

Ethyl (*E*)-2-[*N*-(5-oxo-5-phenylpent-3-enyl)-2-chloroethanamido]propenoate 25c. R_f 0.4 (diethyl ether); ν_{max} (thin film) 2982 (m), 1725 (s), 1670 (s), 1625 (m), 1447 (m), 1406 (m), 1373 (w), 1263 (m), 1228 (m), 1179 (m), 1113 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.94–7.91 and 7.56–7.43 (5H, 2 × m, aromatics), 6.98–6.94 (2H, m, C*H*=C*H*COPh), 6.58 (1H, br s, NC=C*H*), 5.95 (1H, br s, NC=C*H*), 4.28 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.99 (2H, br s, CH_2Cl), 3.73 (2H, t, *J* 6, NCH_2), 2.62–2.58 (2H, m, NCH_2CH_2), 1.32 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 190.0 (COPh), 166.0, 162.9 (NCO and CO_2Et), 144.6 (CH=CHCO), 138.0 (NC=CH_2), 137.2 (aromatic C=CH), 132.6 (CH=CHCO), 128.6 (NC=CH_2), 128.3, 128.0, 127.4 (aromatic C=CH), 62.0 ($CO_2CH_2CH_3$), 46.7 (NCH_2), 41.1 (CH_2Cl), 30.8 (NCH_2CH_2), 14.9 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 352 (M^{37} +

H^+, 46%), 350 ($M^{35} + H^+$, 100), 316 (50) (Found: $M^{35} + H^+$, 350.1156. $C_{18}H_{20}ClNO_4$ requires for $M^{35} + H^+$, 350.1160).

General procedure for the formation of iodides 11c–d, 21a and 25d–f

The chloride (0.97–2.67 mmol) in a saturated solution of sodium iodide (2.91–8.00 mmol) in acetone (40–60 cm^3) was stirred at room temperature overnight. The solvent was evaporated and ethyl acetate (20–40 cm^3) added. This solution was then washed with water, brine, dried (magnesium sulfate) and evaporated to afford the crude product which was purified by column chromatography (silica) to give the iodides as oils (75–99%).

Ethyl (*E*)-2-[*N*-(pent-3-enyl)-2-iodoethanamido]propenoate 11c. R_f 0.5 (diethyl ether–petroleum ether, 2:1); ν_{max} (thin film) 2928 (w), 1725 (s), 1662 (m), 1632 (w), 1299 (w), 1183 (m), 1124 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.57 (1H, s, NC=C*H*), 6.03 (1H, s, NC=C*H*), 5.51–5.32 (2H, m, C*H*=C*H*CH_3), 4.29 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.64 (2H, br s, CH_2I), 3.57–3.45 (2H, m, NCH_2), 2.26–2.18 (2H, m, NCH_2CH_2), 1.65 (3H, d, *J* 6, $CHCH_3$), 1.34 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 166.8, 162.8 (N*C*O and *C*$O_2CH_2CH_3$), 138.2 (N*C*$CO_2CH_2CH_3$), 127.7 (NC=*C*H_2), 127.2, 126.7 (*C*H=*C*HCH_3), 61.6 ($CO_2CH_2CH_3$), 47.2 (NCH_2), 30.0 (NCH_2CH_2), 17.5 (CH_3), 13.7 ($CO_2CH_2CH_3$), −2.9 (CH_2I); *m/z* (CI, NH_3) 369 ($M + NH_4^+$, 55%), 352 ($M + H^+$, 100), 224 (100) (Found: $M + H^+$, 352.0406. $C_{12}H_{18}INO_3$ requires for $M + H^+$, 352.0410).

Ethyl 2-[*N*-(but-3-enyl)-2-iodoethanamido]propenoate 11d. R_f 0.2 (petroleum ether–diethyl ether, 2:1); ν_{max} (thin film) 2933 (m), 1729 (m), 1263 (m), 736 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.62 (1H, s, NC=C*H*), 6.08 (1H, s, NC=C*H*), 5.83–5.66 (1H, m, C*H*=CH_2), 5.17–5.03 (2H, m, CH=CH_2), 4.26 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.75 (2H, s, CH_2I), 3.63–3.46 (2H, m, NCH_2), 2.38–2.23 (2H, m, NCH_2CH_2), 1.33 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 173.7, 162.9 (N*C*O and *C*$O_2CH_2CH_3$), 137.8 (N*C*$CO_2CH_2CH_3$), 134.2 (*C*H=CH_2), 128.7 (CH=*C*H_2), 117.0 (NC=*C*H_2), 62.2 ($CO_2CH_2CH_3$), 47.2 (NCH_2), 31.2 (NCH_2CH_2), 13.9 ($CO_2CH_2CH_3$), −3.7 (CH_2I); *m/z* (CI, NH_3) 355 ($M + NH_4^+$, 95%), 338 ($M + H^+$, 100), 310 (10), 294 (15), 229 (10), 210 (45), 184 (5), 170 (30), 138 (15), 128 (5) (Found: $M + H^+$, 338.0249. $C_{11}H_{16}INO_3$ requires for $M + H^+$, 338.0253).

Ethyl 2-[*N*-(2-cyclohex-1-enylethyl)-2-iodoethanamido]propenoate 21a. R_f 0.25 (petroleum ether–diethyl ether, 2:1); ν_{max} (thin film) 2935 (s), 2871 (w), 1725 (s), 1670 (m), 1446 (w), 1264 (m), 1183 (w), 739 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.55 (1H, s, NC=C*H*), 6.03 (1H, s, NC=C*H*), 5.43 (1H, br s, C=C*H*CH_2), 4.29 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.55 (2H, s, CH_2I), 3.60–3.53 (2H, m, NCH_2), 2.18–2.13 (2H, m, NCH_2CH_2), 1.96–1.89 (4H, m, CH_2C=C*H*CH_2), 1.56–1.49 (4H, m, C=C*H*$CH_2CH_2CH_2$), 1.33 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 167.1, 163.3 (N*C*O and *C*$O_2CH_2CH_3$), 138.6 (N*C*$CO_2CH_2CH_3$), 134.1 (*C*=$CHCH_2$), 127.9 (NC=*C*H_2), 123.2 (C=*C*HCH_2), 62.0 ($CO_2CH_2CH_3$), 46.2 (NCH_2), 35.4 (NCH_2CH_2), 27.9 (CH_2C=CH), 25.1 (C=CH*C*H_2), 22.6, 22.1 (C=C$HCH_2CH_2CH_2$), 14.0 ($CO_2CH_2CH_3$), −2.8 (CH_2I); *m/z* (CI, NH_3) 392 ($M + H^+$, 70%), 266 (100), 224 (10) (Found: $M + H^+$, 392.0722. $C_{15}H_{22}INO_3$ requires for $M + H^+$, 392.0722).

Ethyl (*E*)-2-[*N*-(4-ethoxycarbonylbut-3-enyl)-2-iodoethanamido]propenoate 25d. R_f 0.4 (diethyl ether); ν_{max} (thin film) 1749 (m), 1660 (s), 1548 (m), 1439 (m), 1409 (w), 1375 (m), 1212 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.87 (1H, dt, *J* 16 and 7, C*H*=C$HCO_2CH_2CH_3$), 6.59 (1H, br s, NC=C*H*), 6.04 (1H, br s, NC=C*H*), 5.87 (1H, d, *J* 16, CH=C*H*$CO_2CH_2CH_3$), 4.29 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.18 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.72–3.51 (4H, m, $COCH_2I$ and NCH_2), 2.51 (2H, q, *J* 7, NCH_2CH_2), 1.36 (3H, t, *J* 7, $CO_2CH_2CH_3$), 1.25 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 167.5, 166.0, 163.1 (N*C*O and 2 × *C*O_2Et), 144.5 (*C*H=CHCO$_2CH_2CH_3$), 138.7 (N*C*=CH_2), 128.2 (NC=*C*H_2), 123.4 (CH=*C*$HCO_2CH_2CH_3$), 62.2, 60.2 (2 × $CO_2CH_2CH_3$), 46.8 (NCH_2), 30.0 (NCH_2CH_2), 14.1, 14.0 (2 × $CO_2CH_2CH_3$), −3.3 (CH_2I); *m/z* (CI, NH_3) 427 ($M + NH_4^+$, 100%), 410 ($M + H^+$, 19), 335 (48), 301 (29), 284 (24) (Found: $M + H^+$, 410.0467. $C_{14}H_{20}INO_5$ requires for $M + H^+$, 410.0465).

Ethyl (*E*)-2-[*N*-(5-oxohex-3-enyl)-2-iodoethanamido]propenoate 25e. R_f 0.2 (diethyl ether); ν_{max} (thin film) 2989 (m), 1724 (s), 1665 (s), 1546 (w), 1426 (m), 1370 (m), 1311 (m), 1254 (m), 1182 (m), 1113 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.76 (1H, dt, *J* 16 and 7, C*H*=CHCOCH_3), 6.59 (1H, br s, NC=C*H*), 6.08 (1H, d, *J* 16, CH=C*H*$COCH_3$), 6.05 (1H, br s, NC=C*H*), 4.30 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.72–3.60 (4H, m, $COCH_2I$ and NCH_2), 2.51 (2H, q, *J* 7, NCH_2CH_2), 2.26 (3H, s, $COCH_3$), 1.35 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 198.3 (*C*OCH_3), 167.6, 163.0 (N*C*O and *C*O_2Et), 144.0 (*C*H=CHCOCH_3), 138.3 (CH=*C*$HCOCH_3$), 132.8 (N*C*=CH_2), 128.3 (NC=*C*H_2), 62.1 ($CO_2CH_2CH_3$), 46.2 (NCH_2), 30.5 (NCH_2CH_2), 26.6 ($COCH_3$), 14.0 ($CO_2CH_2CH_3$), −3.3 (CH_2I); *m/z* (CI, NH_3) 397 ($M + NH_4^+$, 100%), 380 ($M + H^+$, 26), 254 (48) (Found: $M + NH_4^+$, 397.0631. $C_{13}H_{18}INO_4$ requires for $M + NH_4^+$, 397.0624).

Ethyl (*E*)-2-[*N*-(5-oxo-5-phenylpent-3-enyl)-2-iodoethanamido]propenoate 25f. R_f 0.4 (diethyl ether); ν_{max} (thin film) 2928 (s), 1723 (s), 1660 (s), 1628 (m), 1288 (m), 1260 (m), 1213 (m), 1179 (m), 1116 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.98–7.85 and 7.51–7.37 (5H, 2 × m, aromatics), 7.01–6.88 (2H, m, C*H*=C*H*COPh), 6.58 (1H, br s, NC=C*H*), 6.05 (1H, br s, NC=C*H*), 4.30 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.75–3.58 (4H, m, CH_2I and NCH_2), 2.66–2.51 (2H, br m, NCH_2CH_2), 1.37 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 190.0 (*C*OPh), 167.8, 163.2 (N*C*O and *C*O_2Et), 145.0 (*C*H=CHCOPh), 138.6 (N*C*=CH_2), 137.4 (aromatic *C*=CH), 132.8 (CH=*C*HCOPh), 128.6 (NC=*C*H_2), 128.6, 128.5, 127.6 (aromatic C=*C*H), 62.3 ($CO_2CH_2CH_3$), 46.8 (NCH_2), 30.7 (NCH_2CH_2), 14.1 ($CO_2CH_2CH_3$), −3.1 (CH_2I); *m/z* (CI, NH_3) 442 ($M + H^+$, 14%), 391 (100), 316 (85) (Found: $M + H^+$, 442.0521. $C_{18}H_{20}INO_4$ requires for $M + H^+$, 442.0515).

General procedure for the tandem radical cyclisation

A 0.014 mol dm^{-3} solution containing tin hydride (0.28–1.59 mmol) and azobisisobutyronitrile (0.03–0.15 mmol) in degassed benzene (20–114 cm^3) was added dropwise over 1 or 5 h *via* a syringe pump to a 0.024 mol dm^{-3} solution of the halide precursor (0.25–1.45 mmol) in degassed benzene (10–60 cm^3) stirred at reflux under nitrogen. After 12 h, the solvent was removed *in vacuo*, diethyl ether (10–20 cm^3) and aqueous potassium fluoride (10% aqueous, 10–20 cm^3) were added. The mixture was stirred for 3 h, the organic layer was separated, dried (magnesium sulfate) and evaporated to afford crude product which was purified by flash column chromatography (silica).

(8a*RS*)-8a-(Ethoxycarbonyl)octahydroindolizin-3-one 17a. R_f 0.25 (diethyl ether); ν_{max} (thin film) 2948 (s), 1730 (s), 1685 (s), 1416 (m), 1265 (m), 1186 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.23 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.16–4.06 (1H, m, NC*H*), 2.80–2.70 (1H, m, NC*H*), 2.55–1.59 (10H, m, $NCH_2CH_2CH_2CH_2$ and $NCOCH_2CH_2$), 1.29 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 174.9, 173.1 (N*C*O and *C*$O_2CH_2CH_3$), 67.2 (N*C*$CO_2CH_2CH_3$), 61.6 ($CO_2CH_2CH_3$), 38.7 (NCH_2), 35.3 ($NCOCH_2CH_2$), 31.7 ($NCOCH_2$), 29.3 ($NCCH_2$), 23.8, 21.6 (NCH_2CH_2 and $NCH_2CH_2CH_2$), 14.2 ($CO_2CH_2CH_3$); *m/z*

(CI, NH_3) 212 (M + H^+, 100%), 168 (10), 150 (5), 138 (70) (Found: M + H^+, 212.1281. $C_{11}H_{17}NO_3$ requires for M + H^+, 212.1287).

(8*R,8a*S**)-8-Methyl-8a-(ethoxycarbonyl)octahydroindolizin-3-one 17b.** R_f 0.3 (diethyl ether); ν_{max} (thin film) 2937 (m), 2876 (m), 1727 (s), 1685 (s), 1453 (m), 1413 (m), 1240 (w), 1183 (w), 1028 (w), 916 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.26–4.14 (2H, m, $CO_2CH_2CH_3$), 4.11–4.04 (1H, m, NC*H*), 3.10–3.01 (1H, m, NC*H*), 2.71 (1H, ddd, *J* 13, 8 and 3, $NCOCH_2CH$), 2.45–2.27 (2H, m, $NCOCH_2$), 1.84–1.36 (6H, m, $NCH_2CH_2CH_2CHCH_3$ and $NCOCH_2CH$), 1.30 (3H, t, *J* 7, $CO_2CH_2CH_3$), 1.04 (3H, d, *J* 6.5, $CHCH_3$); δ_C (67.5 MHz, $CDCl_3$) 173.7, 171.4 (N*C*O and $CO_2CH_2CH_3$), 69.5 ($NCCO_2CH_2CH_3$), 61.1 ($CO_2CH_2CH_3$), 42.3 ($CHCH_3$), 38.0 (NCH_2), 30.7 ($NCOCH_2CH_2$), 29.8 ($NCOCH_2$), 28.9 ($NCH_2CH_2CH_2$), 24.4 (NCH_2CH_2), 16.2 (CH_3), 14.2 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 226 (M + H^+, 65%), 180 (10), 152 (100), 124 (5) (Found: M + H^+, 226.1436. $C_{12}H_{19}NO_3$ requires for M + H^+, 226.1443).

(7*RS*,8a*RS*)-7-Iodo-8a-(ethoxycarbonyl)octahydroindolizin-3-one 19. R_f 0.40 (diethyl ether); ν_{max} (thin film) 2941 (m), 2859 (w), 1728 (s), 1695 (s), 1411 (w), 1250 (w), 1179 (m), 1021 (w), 843 (w), 734 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.24 (2H, q, *J* 7, $CO_2CH_2CH_3$), 4.14–4.02 (1H, tt, *J* 12.5 and 4, C*H*I), 3.97 (1H, ddd, *J* 13.5, 4 and 2, NC*H*), 3.19 (1H, ddd, *J* 13.5, 4 and 2, NC*H*), 2.78 (1H, dt, *J* 2 and 13.5, $NCOCH_2CH$), 2.43–1.88 (7H, m, $NCH_2CH_2CHCH_2$ and $NCOCH_2CH$), 1.30 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 173.9, 172.2 (N*C*O and $CO_2CH_2CH_3$), 68.2 ($NCCO_2CH_2CH_3$), 62.1 ($CO_2CH_2CH_3$), 47.5 ($NCCH_2$), 40.1 (NCH_2), 37.3 (NCH_2CH_2), 30.9 ($NCOCH_2CH_2$), 29.6 ($NCOCH_2$), 18.0 (*C*HI), 14.2 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 355 (M + NH_4^+, 40%), 338 (M + H^+, 90), 294 (5), 283 (10), 266 (75), 229 (25), 212 (100), 192 (15), 181 (20), 164 (25), 155 (5), 138 (15) (Found: M + H^+, 338.0253. $C_{11}H_{16}INO_3$ requires for M + H^+, 338.0252).

(10b*RS*)-3-Oxo-10b-(ethoxycarbonyl)dodecahydropyrrolo-[2,1-*a*]isoquinoline 22. (Found: C, 67.6; H, 8.9; N, 5.0. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.7; N, 5.3%); R_f 0.15 (diethyl ether–petroleum ether, 2:1); ν_{max} (thin film) 2930 (m), 2858 (w), 1726 (s), 1684 (s), 1447 (w), 1413 (m), 1267 (m), 1218 (w), 1182 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.22–4.17 (2H, m, $CO_2CH_2CH_3$), 4.12–4.02 (1H, m, CH-5eq), 3.21–3.12 (1H, m, CH-5ax), 2.76 (1H, ddd, *J* 12.5, 8 and 2.5, CH-1), 2.41–2.27 (2H, m, CH-2), 1.80–1.64 (7H, m, CH-1, CH-6eq, CH-6a, CH-7eq, CH-8eq, CH-9eq and CH-10eq), 1.32–0.89 (9H, m, $CO_2CH_2CH_3$, CH-6ax, CH-7ax, CH-8ax, CH-9ax, CH-10ax, CH-10a); δ_C (67.5 MHz, $CDCl_3$) 173.5, 171.6 (N*C*O and $CO_2CH_2CH_3$), 68.8 (C-11), 61.1 ($CO_2CH_2CH_3$), 52.2 (C-10a), 38.0 (C-5), 35.6 (C-6a), 34.3 (C-7), 32.0 (C-6), 30.9 (C-1), 29.6 (C-2), 26.3 (C-10), 26.1 (C-9), 25.8 (C-8), 14.3 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 383 (M + NH_4^+, 15%), 266 (M + H^+, 100), 192 (25) (Found: M + H^+, 266.1755. $C_{15}H_{23}NO_3$ requires for M + H^+, 266.1756).

Ethyl (2*RS*)-*N*-(2-cyclohex-1-enylethyl)-5-oxopyrrolidine-2-carboxylate 23a. R_f 0.2 (diethyl ether–petroleum ether, 2:1); ν_{max} (thin film) 2924 (s), 2855 (m), 1733 (s), 1658 (s), 1444 (w), 1417 (w), 1329 (w), 1197 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.42 (1H, apparent br s, C=C*H*), 4.28–4.13 (3H, m, $NCHCO_2CH_2CH_3$ and $CO_2CH_2CH_3$), 3.85 (1H, dt, *J* 14 and 8, NC*H*), 2.94 (1H, dt, *J* 14 and 7, NC*H*), 2.53–1.50 (14H, m, NCH_2CH_2, CH_2CH_2C=CHCH_2CH_2 and $NCOCH_2CH_2$), 1.30 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 174.9, 171.9 (N*C*O and $CO_2CH_2CH_3$), 134.5 (*C*=CH), 123.1 (C=*C*H), 61.3 ($CO_2CH_2CH_3$), 59.5 ($NCHCO_2CH_2CH_3$), 39.8 (NCH_2), 35.4 (CH_2C=CH), 29.5, 27.8 ($NCOCH_2$ and NCH_2CH_2), 25.2 (C=CHCH_2), 22.9, 22.7, 22.2 ($NCOCH_2CH_2$ and C=CHCH_2-CH_2CH_2), 14.0 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 266 (M + H^+, 100%), 168 (5) (Found: M + H^+, 266.1756. $C_{15}H_{23}NO_3$ requires for M + H^+, 266.1756).

(1*S*,3*S*,4*R*)-3-Menthyl (2*RS*)-*N*-(2-cyclohex-1-enylethyl)-5-oxopyrrolidine-2-carboxylate 23b. 2.4:1 Mixture of diastereoisomers; R_f 0.3 (diethyl ether–petroleum ether, 2:1); R_T 14.3 min (major isomer); ν_{max} (thin film) 2938 (s), 2867 (w), 1727 (s), 1660 (m), 1441 (w), 1399 (w), 1263 (m), 1182 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) (major isomer) 5.43 (1H, apparent s, C=C*H*), 4.81–4.68 (1H, m, CO_2CH), 4.20 (1H, dd, *J* 8.5 and 3, NC*H*-CO_2CH), 3.94–3.81 (1H, m, NC*H*), 2.96–2.84 (1H, m, NC*H*), 2.52–0.98 (23H, m, NCH_2CH_2, CH_2CH_2C=CHCH_2CH_2, NCO-CH_2CH_2, $CO_2CHCH_2CHCH_2CH_2$ and $CHCH(CH_3)_2$), 0.93 (3H, d, *J* 7, CH_3CHCH_3), 0.91 (3H, d, *J* 7, CH_3CHCH_3), 0.77 (3H, d, *J* 7, $CHCH_3$); δ_C (67.5 MHz, $CDCl_3$) 174.8, 172.9 (N*C*O and CO_2CH), 134.7 (*C*=CH), 123.1 (C=*C*H), 75.6 (CO_2-CH), 59.8 ($NCHCO_2CH$), 46.8 ($CHCH(CH_3)_2$), 40.7, 39.8 (CO_2CHCH_2 and NCH_2), 35.5 (NCH_2CH_2), 34.0 (CH_2C=CH), 31.3 ($CHCH(CH_3)_2$), 29.6 ($NCOCH_2$), 27.8 (C=CHCH_2), 26.8 ($NCOCH_2CH_2$), 26.2 ($CHCH_3$), 25.2, 23.1, 22.7, 22.2 ($CO_2CHCHCH_2CH_2$ and C=CH$CH_2CH_2CH_2$), 21.9, 20.7 ($CH(CH_3)_2$), 17.5 ($CHCH_3$); *m*/*z* (EI) 375 (M^+, 10%), 268 (25), 192 (75), 142 (50), 130 (100), 108 (35), 98 (20), 83 (80), 69 (30), 55 (40) and 41 (25) (Found: M^+, 375.2770. $C_{23}H_{37}NO_3$ requires for M^+, 375.2773). The presence of the minor diastereoisomer was indicated by GC; R_T 14.2 min and ^1H NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 0.75 (3H, d, *J* 7, $CHCH_3$).

(10b*RS*)-3-Oxo-10b-[(1*S*,3*S*,4*R*)-3-menthyloxycarbonyl]-dodecahydropyrrolo[2,1-*a*]isoquinoline 24. 23.5:30.3:9.3:2.3:1.0:1.2 Mixture of diastereoisomers; R_f 0.22 (diethyl ether–petroleum ether, 2:1); R_T 14.4, 14.5, 14.9, 15.3, 15.7 and 15.8 min; ν_{max} (thin film) 2930 (s), 2861 (s), 1715 (s), 1452 (m), 1406 (m), 1264 (m), 1222 (m), 1178 (m) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.73–4.71 (1H, m, CO_2CH), 4.07–4.03 (1H, m, CH-5), 3.20–3.04 (1H, m, CH-5), 2.71–2.68 (1H, m, CH-1), 2.36–2.31 (2H, m, CH-2), 1.98–0.87 (28H, m, CH-1, CH-6, CH-6a, CH-7, CH-8, CH-9, CH-10, CH-10a, 3 × CH_2, $CHCH(CH_3)_2$ and $CHCH_3$), 0.74 and 0.72 (3H, 2 × d, 2 × *J* 7, $CHCH_3$); δ_C (67.5 MHz, $CDCl_3$) (major diastereoisomer) 173.4 , 171.3 (N*C*O and CO_2CH), 75.8 (CO_2CH), 69.0 (C-11), 52.3 (C-10a), 46.8 ($CHCH(CH_3)_2$), 40.8, 38.0 (CO_2CHCH_2 and C-5), 35.6 (C-6a), 34.0, 33.9 (C-7 and $CO_2CHCHCH_2CH_2$), 31.4, 31.1, 30.1 (C-1, C-2 and C-6), 31.2 ($CHCH(CH_3)_2$), 26.5, 25.9 (C-9 and C-10), 26.1 ($CHCH_3$), 22.9, 22.7 ($CO_2CHCHCH_2$ and C-8), 21.9, 20.9 ($CH(CH_3)_2$), 15.8 ($CHCH_3$); *m*/*z* (CI, NH_3) 376 (M + H^+, 100%) 192 (85), 113 (5) (Found: M + H^+, 376.2854. $C_{23}H_{37}NO_3$ requires for M + H^+, 376.2852).

7-(Ethoxycarbonyl)methyl-7a-(ethoxycarbonyl)hexahydro-1*H*-pyrrolizin-3-one 26a. (7*R**,7a*R**) *Major diastereomer*: R_f 0.3 (ethyl acetate); ν_{max} (thin film) 2971 (s), 2934 (m), 1731 (s), 1697 (s), 1398 (m), 1264 (m), 1209 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.28–4.09 (4H, m, 2 × $CO_2CH_2CH_3$), 3.63 (1H, br t, *J* 8, NC*H*), 3.35 (1H, br t, *J* 10, NC*H*), 2.80–2.62 (2H, m, NCC*H* and NCOC*H*), 2.51–2.06 (5H, m, NCOC*H*, NCH_2CH, NC-C*H* and CH_2CO_2), 2.05–1.88 (1H, m, NCC*H*), 1.67–1.63 (1H, m, NCH_2CH), 1.37–1.20 (6H, m, 2 × $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 174.1, 172.0, 171.3 (N*C*O and 2 × CO_2Et), 75.5 ($NCCO_2CH_2CH_3$), 61.6, 60.8 (2 × $CO_2CH_2CH_3$), 45.1 ($NCCHCH_2$), 41.0 (NCH_2), 34.7 ($NCOCH_2$), 34.1 (CH_2-CO_2Et), 32.5 (NCH_2CH_2), 30.9 ($NCCH_2$), 14.2, 14.1 (2 × $CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 284 (M + H^+, 100%), 210 (72) (Found: M + H^+, 284.1498. $C_{14}H_{21}NO_4$ requires for M + H^+, 284.1498).

(7*R**,7a*S**) *Minor diastereomer*: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 3.79–3.71 (1H, m, NC*H*), 3.18–3.07 (1H, m, NC*H*), 2.98–2.91 (1H, m, NCC*H*); δ_C (67.5 MHz, $CDCl_3$) 74.8 ($NCCO_2$), 39.8 ($NCCHCH_2$).

7-(2-Oxopropyl)-7a-(ethoxycarbonyl)hexahydro-1*H*-pyrrolizin-3-one 26b. (7*R**,7a*R**) *Major diastereomer*: R_f 0.15 (ethyl acetate); ν_{max} (thin film) 3100 (w), 1723 (s), 1689 (s), 1406 (w), 1208 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.32–4.11 (2H, m, $CO_2CH_2CH_3$), 3.61 (1H, dt, *J* 11 and 8, NC*H*), 3.32 (1H, br t, *J* 11, NC*H*), 2.69–2.57 (3H, m, NCOC*H*, NCC*H* and C*H*COCH$_3$), 2.51–2.32 (4H, m, NCOC*H*, NCC*H*, NCH$_2$C*H* and C*H*COCH$_3$), 2.22–2.10 (1H, m, NCC*H*), 2.17 (3H, s, COCH_3), 1.93–1.74 (1H, m, NCH$_2$C*H*), 1.41 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 206.4 (*C*OCH$_3$), 174.6, 172.7 (NCO and *C*O$_2$CH$_2$CH$_3$), 76.0 (N*C*CO$_2$CH$_2$CH$_3$), 62.0 ($CO_2CH_2CH_3$), 44.3 (NC*C*H), 44.0 (NCO*C*H$_2$), 41.4 (N*C*H$_2$), 34.6 (*C*H$_2$COCH$_3$), 32.9 (NCH$_2$*C*H$_2$), 31.6 (NC*C*H$_2$), 30.7 (CO*C*H$_3$), 14.7 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 254 (M + H^+, 100%), 180 (20) (Found: M + H^+, 254.1390. $C_{13}H_{19}NO_4$ requires for M + H^+, 254.1392).

(7*R**,7a*S**) *Minor diastereomer*: R_f 0.1 (ethyl acetate); ν_{max} (thin film) 3097 (w), 1721 (m), 1693 (s), 1384 (w), 1294 (w), 1210 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.32 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.79–3.61 (1H, m, NC*H*), 3.09 (1H, ddd, *J* 1.5, 9.5 and 16, NC*H*), 2.91–2.02 (1H, m, NCC*H*), 2.79–2.60 (2H, m, NCOC*H* and C*H*COCH$_3$), 2.46–2.15 (4H, m, NCOC*H*, NCC*H*, NCH$_2$C*H* and C*H*COCH$_3$), 2.17 (3H, s, COCH_3), 1.97–1.85 (1H, m, NCC*H*), 1.57–1.43 (1H, m, NCH$_2$C*H*), 1.30 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 206.1 (*C*OCH$_3$), 175.3, 173.7 (N*C*O and *C*O$_2$CH$_2$CH$_3$), 74.6 (N*C*CO$_2$CH$_2$CH$_3$), 61.8 ($CO_2CH_2CH_3$), 43.7 (NCO*C*H$_2$), 41.5 (N*C*H$_2$), 38.8 (NC*C*H), 33.4 (*C*H$_2$COCH$_3$), 32.5 (NCH$_2$*C*H$_2$), 30.3 (NC*C*H$_2$), 27.2 (CO*C*H$_3$), 14.2 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 254 (M + H^+, 100%), 180 (20) (Found: M + H^+, 254.1396. $C_{13}H_{19}NO_4$ requires for M + H^+, 254.1392).

7-(2-Oxo-2-phenylethyl)-7a-(ethoxycarbonyl)hexahydro-1*H*-pyrrolizin-3-one 26c. (7*R**,7a*R**) *Major diastereomer*: R_f 0.1 (diethyl ether); ν_{max} (thin film) 3038 (w), 2708 (s), 1832 (s), 1768 (w), 1677 (s), 1579 (s), 1526 (s), 1477 (s), 1397 (s), 1003 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.99–7.87 and 7.64–7.40 (5H, m, aromatics), 4.34–4.10 (2H, m, $CO_2CH_2CH_3$), 3.67 (1H, dt, *J* 8.5 and 11, NC*H*), 3.43–3.32 (1H, m, NC*H*), 2.81–2.63 (3H, m, NCOC*H*, NCC*H* and C*H*COPh), 2.57–2.19 (5H, m, NCOC*H*, NCCH_2, NCH$_2$C*H* and C*H*COPh), 2.03–1.89 (1H, m, NCH$_2$C*H*), 1.16 (3H, t, *J* 7, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 197.4 (*C*OPh), 174.1, 172.2 (N*C*O and *C*O$_2$CH$_2$CH$_3$), 136.4 (aromatic *C*=CH), 133.3, 128.6, 127.8 (aromatic C=*C*H), 75.7 (N*C*CO$_2$CH$_2$CH$_3$), 61.5 ($CO_2CH_2CH_3$), 44.1 (NC*C*H), 41.0 (N*C*H$_2$), 38.7 (NCO*C*H$_2$), 34.1 (*C*H$_2$COPh), 32.6 (NCH$_2$*C*H$_2$), 31.1 (NC*C*H$_2$), 14.1 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 316 (M + H^+, 100%), 242 (75) (Found: M + H^+, 316.1544. $C_{18}H_{21}NO_4$ requires for M + H^+, 316.1549).

(7*R**,7a*S**) *Minor diastereomer*: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 3.82–3.73 (1H, m, NC*H*), 3.01–2.87 (2H, m, NC*H* and NCC*H*), 1.63–1.52 (1H, m, NCH$_2$C*H*); δ_C (67.5 MHz, $CDCl_3$) 175.1, 173.4 (N*C*O and *C*O$_2$CH$_2$CH$_3$), 133.4, 128.7, 127.9 (aromatic C=*C*H), 74.8 (N*C*CO$_2$CH$_2$CH$_3$), 61.7 ($CO_2CH_2CH_3$), 41.3 (N*C*H$_2$), 39.1 (NC*C*H), 38.8 (NCO*C*H$_2$), 33.4 (*C*H$_2$COPh), 27.2 (NC*C*H$_2$).

Ethyl (2*RS*)-*N*-[(*E*)-4-ethoxycarbonylbut-3-enyl]pyroglutamate 27. R_f 0.45 (diethyl ether); ν_{max} (thin film) 2930 (m), 1776 (s), 1737 (s), 1297 (m), 1268 (m), 1178 (m), 1119 (w), 1039 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.88 (1H, dt, *J* 16 and 7, C*H*=CHCO$_2$CH$_2$CH$_3$), 5.90 (1H, d, *J* 16, CH=C*H*CO$_2$CH$_2$CH$_3$), 4.37–4.11 (5H, m, NC*H*CO$_2$CH$_2$CH$_3$ and 2 × CO$_2$C*H*$_2$CH$_3$), 3.51–3.39 (1H, m, NC*H*CH$_2$), 3.31–3.20 (1H, m, NC*H*CH$_2$), 2.74–2.57 (2H, m, NCOC*H*$_2$), 1.77–1.58 (4H, m, C*H*$_2$CH=CH and NCHC*H*$_2$), 1.42–1.17 (6H, m, 2 × CO$_2$CH$_2$C*H*$_3$); *m*/*z* (CI, NH_3) 301 (M + NH_4^+, 64%), 284 (M + H^+, 100), 272 (55), 238 (31) (Found: M + H^+, 284.1497. $C_{14}H_{21}NO_5$ requires for M + H^+, 284.1498).

(2*RS*,3*RS*)-1-Ethanoyl-2-(ethoxycarbonyl)-2-[(tributylstannyl)methyl]-3-[(ethoxycarbonyl)methyl]pyrrolidine 28a. R_f 0.8 (diethyl ether); ν_{max} (thin film) 2955 (s), 2871 (s), 1778 (w), 1735 (s), 1652 (w), 1594 (m), 1461 (m), 1271 (m), 1189 (m), 1113 (w), 1027 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.28–4.02 (4H, m, 2 × CO$_2$C*H*$_2$CH$_3$), 3.84–3.75 (1H, m, NC*H*), 3.72–3.61 (1H, m, NC*H*), 2.85–2.52 (3H, m, C*H*CH$_2$CO$_2$CH$_2$CH$_3$), 2.08 (3H, s, NCOCH_3), 1.82–1.58 (4H, m, NCH$_2$CH_2 and NCCH_2), 1.54–1.16 [24H, m, 3 × Sn(CH_2)$_3$CH$_3$ and 2 × CO$_2$CH$_2$CH_3], 0.88 [9H, t, *J* 7, 3 × Sn(CH$_2$)$_3$CH_3]; *m*/*z* (CI, NH_3) 574 (M^{118} + H^+, 47%), 572 (M^{116} + H^+, 26) and 518 (100) (Found: M^{116} + H^+, 572.2711. $C_{26}H_{49}NO_5Sn$ requires for M^{116} + H^+, 572.2706).

(2*RS*,3*RS*)-1-Ethanoyl-2-(ethoxycarbonyl)-2-[(triphenylstannyl)methyl]-3-[(ethoxycarbonyl)methyl]pyrrolidine 28b. R_f 0.5 (diethyl ether); ν_{max} (thin film) 3005 (s), 1733 (s), 1630 (m), 1427 (m), 1255 (w), 1153 (m), 1026 (w), 731 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.74–7.22 (15H, m, aromatics), 4.17–4.01 (4H, m, 2 × CO$_2$C*H*$_2$CH$_3$), 3.56–3.44 (2H, m, NC*H*$_2$), 2.94–2.82 (1H, m, NCC*H*), 2.68–2.51 (2H, m, CHC*H*$_2$CO$_2$CH$_2$CH$_3$), 2.33–2.21 (1H, m, NCC*H*), 2.09 (3H, s, NCOCH_3), 2.01–1.82 (2H, m, NCH$_2$C*H* and NCC*H*), 1.78–1.62 (1H, m, NCH$_2$C*H*), 1.28 (6H, t, *J* 6, 2 × CO$_2$CH$_2$CH_3); *m*/*z* (CI, NH_3) 634 (M^{118} + H^+, 4%), 632 (M^{116} + H^+, 2), 558 (100), 557 (45), 556 (75), 554 (43) (Found: M^{116} + H^+, 632.1771. $C_{32}H_{37}NO_5Sn$ requires for M^{116} + H^+, 632.1767).

(2*RS*,3*RS*)-1-Ethanoyl-2-(ethoxycarbonyl)-2-[(tributylstannyl)methyl]-3-(2-oxopropyl)pyrrolidine 28c. R_f 0.6 (diethyl ether); ν_{max} (thin film) 2955 (s), 2925 (s), 1726 (m), 1653 (w), 1410 (w), 1199 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.16 (2H, q, *J* 7, $CO_2CH_2CH_3$), 3.71–3.62 (1H, m, NC*H*), 3.57–3.45 (1H, m, NC*H*), 2.70 (1H, dd, *J* 7.5 and 2.5, C*H*COCH$_3$), 2.52–2.41 (1H, m, C*H*CH$_2$COCH$_3$), 2.17 (3H, s, CH$_2$COCH_3), 2.21–2.07 (2H, m, C*H*COCH$_3$ and NCC*H*), 2.02 (3H, s, NCOCH_3), 1.71–1.56 (3H, m, NCC*H* and NCH$_2$CH_2), 1.55–1.17 [21H, m, 3 × Sn(CH_2)$_3$CH$_3$ and CO$_2$CH$_2$CH_3], 0.79 [9H, t, *J* 7, 3 × Sn(CH$_2$)$_3$CH_3]; δ_C (67.5 MHz, $CDCl_3$) 206.1 (*C*OCH$_3$), 173.7, 169.5 (N*C*O and *C*O$_2$CH$_2$CH$_3$), 71.2 (N*C*CO$_2$CH$_2$CH$_3$), 61.1 ($CO_2CH_2CH_3$), 48.1 (N*C*H$_2$), 45.8 (*C*HCH$_2$COCH$_3$), 43.6 (NC*C*H$_2$), 30.4 (CO*C*H$_3$), 27.9 (*C*H$_2$COCH$_3$), 29.3, 27.5, 26.8 (NCH$_2$*C*H$_2$ and SnCH$_2$*C*H$_2$*C*H$_2$CH$_3$), 23.4 (NCO*C*H$_3$), 14.4 ($CO_2CH_2CH_3$), 13.7 (SnCH$_2$CH$_2$CH$_2$*C*H$_3$), 9.9 (Sn*C*H$_2$CH$_2$CH$_2$CH$_3$); *m*/*z* (CI, NH_3) 544 (M^{118} + H^+, 32%), 542 (M^{116} + H^+, 40), 488 (43), 487 (19), 486 (33), 484 (10), 256 (100) (Found: M^{116} + H^+, 542.2604. $C_{25}H_{47}NO_4Sn$ requires for M^{116} + H^+, 542.2601).

(2*RS*,3*RS*)-1-Ethanoyl-2-(ethoxycarbonyl)-2-[(triphenylstannyl)methyl]-3-(2-oxopropyl)pyrrolidine 28d. R_f 0.6 (dichloromethane–ethyl acetate; 7 : 3); ν_{max} (thin film) 2955 (s), 2933 (s), 1725 (s), 1629 (m), 1426 (m), 1265 (m), 1198 (m), 734 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.70–7.41 and 7.38–7.21 (15H, m, aromatics), 4.10 (2H, q, *J* 7, CO$_2$C*H*$_2$CH$_3$), 3.51–3.39 (1H, q, *J* 10, NC*H*), 2.97 (1H, dt, *J* 10 and 7, NC*H*), 2.85–2.70 (1H, m, C*H*CH$_2$COCH$_3$), 2.65–2.54 (4H, m, CH_2COCH$_3$ and SnCH_2), 2.08–1.95 (NCH$_2$C*H*), 2.05 (3H, s, CH$_2$COCH_3), 1.98 (3H, s, NCOCH_3), 1.58–1.47 (1H, m, NCH$_2$C*H*), 1.37 (3H, t, *J* 7, CO$_2$CH$_2$CH_3); δ_C (67.5 MHz, $CDCl_3$) 205.9 (*C*OCH$_3$), 173.0, 169.9 (N*C*O and *C*O$_2$CH$_2$CH$_3$), 140.4, 137.0, 128.5, 128.2 (aromatic *C*=CH and C=*C*H), 70.8 (N*C*CO$_2$CH$_2$CH$_3$), 61.4 ($CO_2CH_2CH_3$), 47.8 (N*C*H$_2$), 46.7 (*C*HCH$_2$COCH$_2$CH$_3$), 43.5 (NC*C*H$_2$), 30.3 (NCH$_2$*C*H$_2$), 30.1 (CO*C*H$_3$), 29.1 (*C*H$_2$COCH$_3$), 21.6 (NCO*C*H$_3$), 14.2 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 604 (M^{118} + H^+, 7%), 602 (M^{116} + H^+, 3), 528 (100), 527 (44), 526 (74), 524 (40) (Found: M^{116} + H^+, 602.1663. $C_{31}H_{35}NO_4Sn$ requires for M^{116} + H^+, 602.1661).

Ethyl (2*RS*)-2-[(*E*)-*N*-(4-ethoxycarbonylbut-3-enyl)ethanamido]-3-(tributylstannyl)propanoate 29. R_f 0.9 (diethyl ether); ν_{max} (thin film) 1779 (s), 1722 (s), 1665 (w), 1448 (w), 1370 (w),

1262 (m), 1192 (m), 1114 (m), 1032 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.92–6.75 (1H, dt, *J* 7 and 16, C*H*=CHCO$_2$CH$_2$CH$_3$), 5.95–5.87 (1H, d, *J* 16, CH=C*H*CO$_2$CH$_2$CH$_3$), 4.37–4.11 (5H, m, NC*H*CO$_2$Et and 2 × CO$_2$C*H*$_2$CH$_3$), 3.76–3.59 (2H, m, NC*H*$_2$CH$_2$), 2.04 (3H, s, NCOC*H*$_3$), 1.84–1.67 (4H, m, NCC*H*$_2$ and NCH$_2$C*H*$_2$), 1.54–1.12 [24H, m, 3 × Sn(C*H*$_2$)$_3$CH$_3$ and 2 × CO$_2$CH$_2$C*H*$_3$], 0.77 [9H, t, *J* 7, 3 × Sn(CH$_2$)$_3$C*H*$_3$]; *m*/*z* (CI, NH_3) 574 (M^{118} + H^+, 46%), 572 (M^{116} + H^+, 27), 518 (100), 517 (44), 516 (75), 515 (33), 514 (43) (Found: M^{116} + H^+, 572.2699. $C_{26}H_{49}NO_5Sn$ requires for M^{116} + H^+, 572.2706).

Ethyl 2-[(*E*)-*N*-(5-oxo-5-phenylpent-3-enyl)ethanamido]propenoate 30. R_f 0.2 (diethyl ether); ν_{max} (thin film) 2930 (m), 1729 (s), 1670 (s), 1631 (m), 1448 (w), 1406 (w), 1372 (w), 1215 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.99–7.87 and 7.61–7.37 (5H, m, aromatics), 7.01–6.95 (2H, m, C*H*=C*H*COPh), 6.48 (1H, br s, NC=C*H*), 5.75 (1H, br s, NC=C*H*), 4.31–4.11 (2H, q, *J* 7, CO$_2$C*H*$_2$CH$_3$), 3.73 (2H, t, *J* 7, NC*H*$_2$), 2.67–2.54 (2H, m, NCH$_2$C*H*$_2$), 1.98 (3H, s, NCOC*H*$_3$), 1.24 (3H, t, *J* 7, CO$_2$CH$_2$C*H*$_3$); *m*/*z* (CI, NH_3) 316 (M + H^+, 100%), 274 (25), 159 (20), 105 (35) (Found: M + H^+, 316.1542. $C_{18}H_{21}NO_4$ requires for M + H^+, 316.1549).

(2*RS*,3*RS*)-1-(2-Chloroethanoyl)-2-(ethoxycarbonyl)-2-[(tributylstannyl)methyl]-3-(2-oxopropyl)pyrrolidine 32. R_f 0.7 (diethyl ether); ν_{max} (thin film) 2910 (s), 1727 (m), 1657 (w), 1417 (w), 1267 (w), 1198 (w), 737 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.20–4.09 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.96 (2H, s, NCOC*H*$_2$Cl), 3.85–3.78 (1H, m, NC*H*), 3.67–3.51 (1H, m, NC*H*), 2.72 (1H, dd, *J* 7.5 and 2.5, C*H*COCH$_3$), 2.55–2.43 (1H, m, C*H*CH$_2$COCH$_3$), 2.29–2.14 (2H, m, NCC*H* and C*H*COCH$_3$), 2.17 (3H, s, COCH$_3$), 1.78–1.61 (3H, m, NCC*H* and NCH$_2$C*H*$_2$), 1.57–1.14 (21H, m, 3 × SnC*H*$_2$C*H*$_2$C*H*$_2$CH$_3$ and CO$_2$CH$_2$C*H*$_3$), 0.80 (9H, t, *J* 7, 3 × SnCH$_2$CH$_2$CH$_2$C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 205.9 (*C*OMe), 164.8, 172.9 (N*C*O and *C*O$_2$CH$_2$CH$_3$), 72.1 (N*C*CO$_2$CH$_2$CH$_3$), 61.4 (CO$_2$*C*H$_2$CH$_3$), 47.4 (NCH$_2$), 45.4 (NC*C*H), 43.4 (NC*C*H$_2$), 30.4 (CO*C*H$_3$), 29.2 (*C*H$_2$COCH$_3$), 27.8 (NCH$_2$*C*H$_2$), 29.1, 27.4 (SnCH$_2$*C*H$_2$*C*H$_2$CH$_3$), 14.3 (CO$_2$CH$_2$*C*H$_3$), 13.8, 10.0 (Sn*C*H$_2$CH$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 578 ($M^{118,35}$ + H^+, 10%), 576 ($M^{116,35}$ + H^+, 5), 546 (27), 545 (14), 544 (20), 543 (13), 488 (33), 487 (14), 486 (25), 484 (14), 256 (100) (Found: $M^{116,35}$ + H^+, 576.2209. $C_{25}H_{46}ClNO_4Sn$ requires for $M^{116,35}$ + H^+, 576.2211).

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