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Synthesis of 3-Alkylpyrrolidines by Anionic Cyclization

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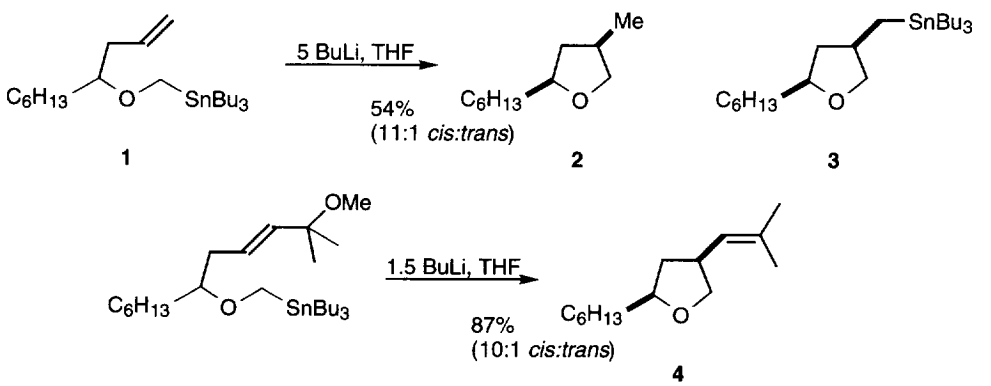
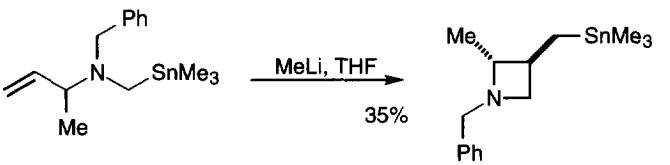
Abstract: α-Aminocarbanions, generated by transmetallation of aminomethylstannanes, cyclize onto an unactivated alkene to give 3-alkylpyrrolidines. The intermediate organolithium either reincorporates trimethyltin or, from the tributylstannanes, can be trapped with a variety of electrophiles. From the trimethylstannane, the cyclization can be promoted catalytically using 0.2 equivalents of methyllithium. The trimethyltin group in the product can be cleaved using ceric ammonium nitrate. Trapping the 3-lithiomethylpyrrolidine with ethylchloroformate, followed by hydrolysis provides a four step synthesis of the GABA uptake inhibitor 3-pyrrolidineacetic acid.

Despite the now well-known propensity for a carbanion to cyclize onto an unactivated alkene,[1-3] there are few reports of the formation of oxygen-containing[4,5] or nitrogen-containing[4b-9] heterocycles by such an anionic cyclization. Herein we report full details of our procedure for the synthesis of pyrrolidines, which uses tin-lithium exchange to generate an α-aminocarbanion. The carbanion cyclizes onto an unactivated alkene to give a new organolithium species. The cyclization proceeds through a two-electron process, in which the metal coordinates to the alkene prior to cyclization.[1,9] Both Broka[4] and, recently, Lautens[5] have reported anionic cyclizations with the use of tin-lithium exchange for carbanion formation. In Broka's work, the 3-methyltetrahydrofuran **2** is obtained by treating the stannane **1** with excess *n*-butyllithium. On using only a slight excess of *n*-butyllithium, the tetrahydrofuran **2** is formed in low yield, together with trace amounts of the stannane **3**.[4] Improved yields were obtained when a methoxy substituent was positioned such that elimination of methoxide gave the 3-vinyltetrahydrofuran **4**. Lautens[5] has reported more elaborate versions of this cyclization to tetrahydrofurans and extended it, in a single example, to the preparation of a pyrrolidine-containing bicyclic product.



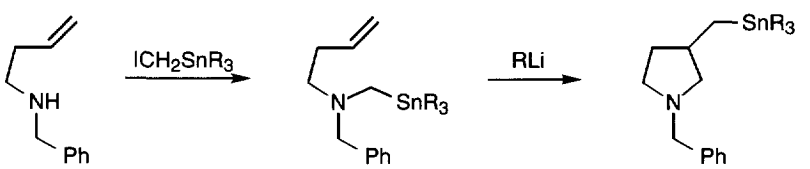
1 **2** **3** **4**

While investigating the aza-Wittig rearrangement,[7,10] we discovered that, on treatment of the aminomethylstannane **5** with methyllithium, an anionic cyclization to the azetidine **6** took place (rather than a 1,2- or 2,3-sigmatropic shift). This unexpected result demonstrates the ability of carbanions to cyclize by a 4-*exo-trig* process to give four-membered rings. In addition, no 2,3-dimethylazetidine was obtained, but the tin group had been reincorporated to give 2-methyl-3-stannylmethylazetidine **6**. The cyclization was stereoselective, with formation only of the isomer *trans* **6**.



5 **6**

In a similar way to the formation of the tetrahydrofuran **3**, observed by Broka[4] as a by-product, azetidine **6** must arise by i) transmetallation of the aminomethylstannane **5** to the corresponding aminomethyllithium, ii) anionic cyclization onto the unactivated alkene and iii) recapture of the azetidinylmethyl anion with a trimethyltin group. As a consequence of this result, we began an investigation of the potential of anionic cyclizations for the formation of cyclic amines. We began our studies with homoallylic amines rather than allylic amines, as this would lead to the more common pyrrolidine ring. In addition, the 5-*exo-trig* pathway ought to be a more favoured cyclization than 4-*exo-trig*. The required aminomethylstannanes **8**, R=Me,Bu were prepared by alkylation of the secondary amine *N*-benzyl-4-amino-1-butene **7** with iodomethyltrimethyltin or iodomethyltributyltin.[11] These alkylations gave satisfactory yields of the stannanes **8** at room temperature in acetonitrile or acetone, with potassium carbonate as the base. The aminomethylstannanes **8** decompose slowly on silica gel and purification is best achieved by rapid chromatography on neutral or basic alumina.



7 **8** **9**

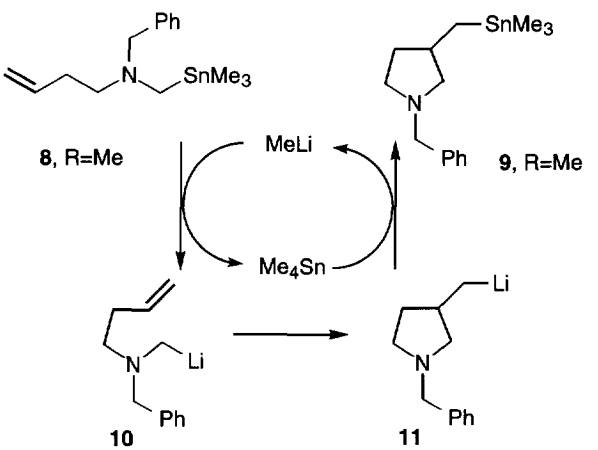
Table 1 Anionic cyclization of trimethylstannane 8, R=Me

Entry	*Solvent*	*Conditions*	*Yield (%)*
1	THF	-78 to 0 °C	55
2	THF, TMEDA	-45 to 0 °C	51
3	TMEDA	-45 to 0 °C	44
4	DME	-45 to 0 °C	47
5	Diglyme	-45 to 0 °C	41
6	Et_2O	-78 °C to room temp.	16[a]
7	Hexane	-78 °C to room temp.	—
8	Hexane-Et_2O (3:2)	-78 °C to room temp.	40[a]
9	Hexane-Et_2O (10:1)	-78 °C to room temp.	12[a]
10	THF (2 equiv. $SnMe_4$)	-78 to 0 °C	72

[a]Pyrrolidine **16** was also isolated (19-47%)

Treatment of the stannane **8**, R=Me with one equivalent of methyllithium gave, as expected, the pyrrolidine **9**, R=Me. The trimethyltin group had been reincorporated after the anionic cyclization. The best solvent for the cyclization, from the selection chosen in Table 1, appears to be THF. The use of TMEDA to promote anionic cyclization has been documented by Bailey,[1] although with substrate **8**, R=Me we observed no significant alteration in reaction rate or product yield when transmetallation-anionic cyclization was carried out in TMEDA or THF/TMEDA mixtures (Entries 2 and 3). Tin-lithium exchange and anionic cyclization occur rapidly at -78 °C in polar solvents such as THF. In the apolar solvent hexane, no transmetallation took place, however, the use of hexane-diethylether (10:1) (Entry 9) did allow transmetallation and cyclization, although the yield of the pyrrolidine **9**, R=Me was low, presumably due to the slow reincorporation of the trimethyltin group in the less polar solvent mixture. In contrast to the use of THF as the solvent, the use of the less polar hexane-diethylether solvent mixtures necessitated that the solution be warmed above 0 °C for transmetallation (and hence cyclization) to occur. No products resulting from 1,2-Wittig rearrangement of the *N*-benzyl group were observed. The addition of two equivalents of tetramethyltin (Entry 10) improves the yield of the pyrrolidine **9**, R=Me. This result suggests that the origin of the tin group in the pyrrolidine **9** is from tetramethyltin, which would be generated in the initial transmetallation of stannane **8**, R=Me, with methyllithium.

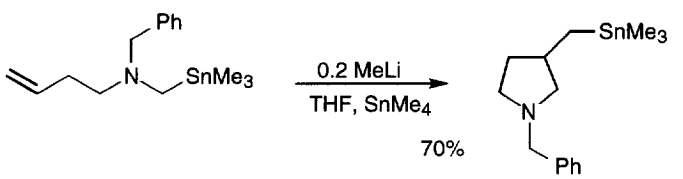
The transformation of aminomethylstannane **8**, R=Me into pyrrolidine **9**, R=Me occurs presumably by way of the aminomethyllithium **10**. Cyclization onto the alkene results in the formation of the organolithium **11**, which reincorporates the trimethyltin group to give the product **9**, R=Me. Attack of the organolithium **11** onto tetramethyltin releases the product pyrrolidine **9**, R=Me and methyllithium, which can continue the cycle.



Transmetallation of the stannane **8**, R=Me, with methyllithium in THF is thought to proceed *via* a pentacoordinate stannate anion.[12] This species can break down either to regenerate methyllithium and the stannane **8**, R=Me, or by release of tetramethyltin and the organolithium **10**. The presence of a heteroatom on the α- carbon of an organolithium is known to stabilise the organolithium through chelation (intra and/or intermolecular) of the lithium atom with the lone pair(s) of the heteroatom.[13] This would favour release of the more stable α-amino-substituted carbanion **10** and generation of tetramethyltin. Anionic cyclization to the organolithium **11** is a favourable isomerism, presumably due to the gain of a carbon-carbon σ-bond at the expense of a carbon-carbon π-bond, despite the formation of a less stable organolithium. Lithium atom coordination to the alkene[14] followed by insertion of the carbon-lithium bond across the alkene would generate

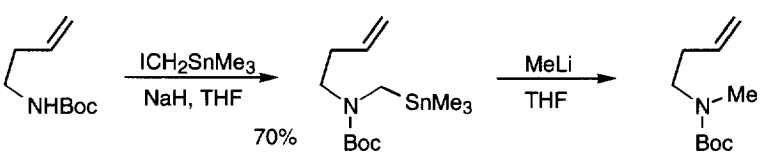
the pyrrolidine **11**. This new organolithium **11** could reincorporate the trimethyltin group either from the starting stannane **8**, R=Me, or from the tetramethyltin generated in the initial transmetallation to the aminomethyllithium **10**. Addition of the organolithium **11** to tetramethyltin would give an intermediate stannate complex, which would be expected to release methyllithium, rather than regenerate the more substituted alkyllithium **11**, which would be less stable than methyllithium.[15]

Pyrrolidine **9**, R=Me is an isomer of the stannane **8**, R=Me and this transformation could, in theory, be promoted catalytically with methyllithium. In practice, the amount of methyllithium that allows the formation of the pyrrolidine **9**, R=Me without significant reduction in yield is of the order of 20-40 mol%. Reducing the amount of methyllithium further results in some recovered stannane **8**, R=Me. When the rearrangement was conducted with 0.4 equivalents of methyllithium (THF, -78 °C to 0 °C), the pyrrolidine **9**, R=Me was isolated (54%). The use of only 0.2 equivalents of methyllithium in the presence of $SnMe_4$ (THF, -78 °C to 0 °C) gave the pyrrolidine **9**, R=Me (70%). The reduction to substoichiometric quantities of methyllithium to allow a catalytic cycle is a valuable facet of this cyclization and demonstrates the potential worth of such anionic cyclizations.



8, R=Me **9**, R=Me

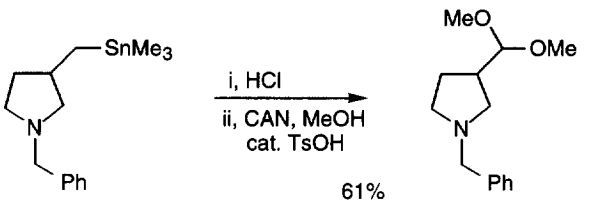
Anionic cyclization of the aminomethylstannane **8**, R=Me with methyllithium acting as a catalyst proceeds in good yield to give the pyrrolidine **9**, R=Me. On the other hand, attempts to cyclize the amidomethylstannane **13**, formed by alkylation of the carbamate **12** (prepared by Curtius rearrangement of 4-pentenoic acid with diphenylphosphorylazide), gave only the protodestannylated carbamate **14**. It appears that the added stabilization imparted by the *tert*-butyloxycarbonyl group is sufficient to prevent the cyclization. This may arise from chelation of the lithium atom to the carbonyl oxygen atom, thereby disfavouring anionic cyclization onto the alkene π-bond.



12 **13** **14**

The formation of pyrrolidine **9**, R=Me from aminomethylstannane **8**, R=Me allows access to one 3-substituted pyrrolidine. Attempts to transmetallate pyrrolidine **9**, R=Me with methyllithium, in order to prepare a variety of functionalized pyrrolidines, only led to recovered starting material. There are a number of reports in the literature of the conversion of tetraalkylstannanes to other functional groups, including the use of ceric ammonium nitrate (CAN),[16] bromine followed by mCPBA,[17] ozone,[18] iodosylbenzene[19] and chromium trioxide-pyridine complex.[20] Treatment of the pyrrolidine **9**, R=Me with each of these reagents led to decomposition or the recovery of starting material, except for the use of CAN in methanol, which gave the pyrrolidine **15** (25%). The mechanism for the formation of pyrrolidine **15** presumably proceeds *via* methanol

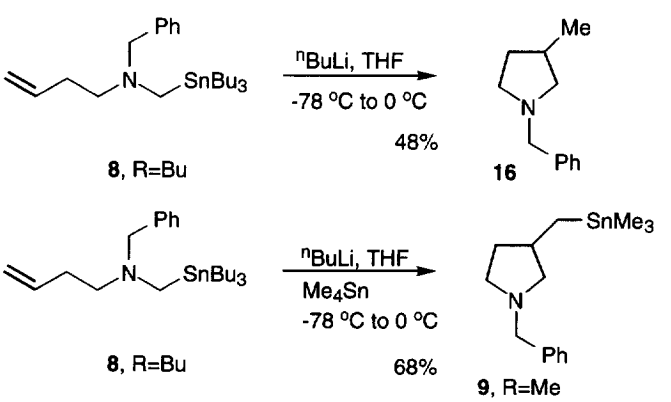
addition to the precursor aldehyde (probably formed from a nitrate ester intermediate). We considered that the addition of acid may improve the yield of **15** by catalyzing acetal formation. The addition of *para*-toluenesulfonic acid (TsOH) to the reaction did increase the yield of the pyrrolidine **15** to 37%. The yield could be improved further by protection the amine nitrogen atom (presumably from oxidation by CAN), by addition of ethereal hydrochloric acid prior to treatment with CAN. This resulted in the isolation of pyrrolidine **15**, in which the yield had increased to 61%. The successful transformation of the pyrrolidine **9**, R=Me to the pyrrolidine **15** opens the way for the preparation of a variety of 3-substituted pyrrolidines.



9, R=Me **15**

The use of tin in organic synthesis is normally associated with tributyltin derivatives, rather than trimethyltin compounds. This is due to their relative cost and the increased volatility of tetramethyltin over tetrabutyltin (and hence the increased toxicity risk). Having demonstrated the effectiveness of the use of the trimethylstannane **8**, R=Me for pyrrolidine synthesis, we wished to investigate the effect of the change to the tributyltin derivative **8**, R=Bu. In comparison with the work of Broka[4] (cyclization of the stannane **1**), we expected that the stannane **8**, R=Bu would undergo anionic cyclization, but without reincorporation of the tributyltin group.

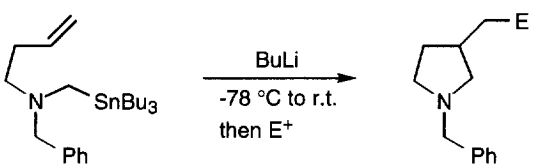
Treatment of the stannane **8**, R=Bu with *n*-butyllithium (or methyllithium) gave the pyrrolidine **16**, with very little (<10%) of the pyrrolidine **9**, R=Bu. This result indicates that both transmetallation to the organolithium **10** and anionic cyclization to the pyrrolidine **11** occur easily. Reincorporation of the tin group takes place only to a minor extent, probably because of the steric bulk of the tributyltin group.[21] Unlike transmetallation of the stannane **1**,[4] it was not necessary to add an excess of *n*-butyllithium in order to promote formation of the pyrrolidine **16**. From the trimethylstannane **8**, R=Me, the yield of the pyrrolidine **9**, R=Me was improved on addition of two equivalents of tetramethyltin (Table 1, entry 10). The addition of two equivalents of tetramethyltin to the stannane **8**, R=Bu, immediately following transmetallation, resulted in the formation of the pyrrolidine **9**, R=Me in good yield. This result clearly indicates that the trimethyltin group can be reincorporated from tetramethyltin and that this occurs more easily than reincorporation of the tributyltin group.



8, R=Bu **16**

8, R=Bu **9**, R=Me

The incorporation of the trimethyltin group to give the pyrrolidine **9**, R=Me from the stannane **8**, R=Bu, suggests that the intermediate organolithium **11** can be trapped with electrophiles other than trimethyltin. Attempts to transmetallate the stannane **8**, R=Bu (using ^{n}BuLi, THF, -78 °C), followed by the addition of a variety of electrophiles did give rise to the desired pyrrolidines **17** (Table 2), together with some 3-methylpyrrolidine **16**. The formation of pyrrolidine **16** arises despite careful attempts to rigorously exclude moisture from the reaction. It is likely that the source of the proton is the solvent THF, which, at temperatures significantly above -78 °C has been reported to protonate alkyllithiums.[22] The use of less polar solvents would avoid the problem of the formation of pyrrolidine **16**. As the stannanes **8** do not transmetallate in hexane alone, the reactions were conducted in the presence of some diethylether. The yield of the pyrrolidine **17a** increased as the amount of diethylether was reduced (entries 3-5) and optimum conditions involved the use of hexane:diethylether (10:1). In this solvent system transmetallation occurs above 0 °C and the reaction mixture was allowed to stand at room temperature for 1-3 h to allow complete transmetallation and anionic cyclization, before the addition of the electrophile (at -78 °C). Despite the warmer reaction temperature, very little or no pyrrolidine **16** was isolated under these conditions. The intermediate organolithium **11** could be trapped with a variety of electrophiles (Table 2), including MeOH, CD_3OD, allyl bromide, benzophenone and various aldehydes, including aldehydes containing enolisable protons (such as acetaldehyde, entry 13). The product aminoalcohols **17e-h**, formed by trapping with aldehydes, were fairly unstable to silica gel, but could be purified by column chromatography on neutral alumina. The aminoalcohols **17a** and **17e-h** were isolated as mixtures of the two possible diastereomers in ratios of 1:1 to 2:1.



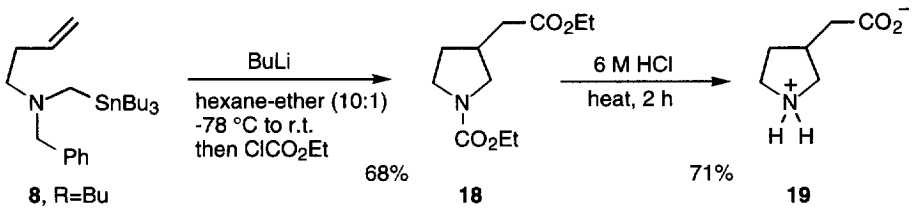
8, R=Bu **17**

Table 2 Anionic cyclization of tributylstannane 8, R=Bu

Entry	*Solvent*	*Electrophile, E+*	*E*	*Product*	*Yield (%)* **17**
1	THF	Me_4Sn[a]	$SnMe_3$	**9**, R=Me	68
2	THF	PhCHO	CH(OH)Ph	**17a**	17[b]
3	Hexane-ether (1:5)	PhCHO	CH(OH)Ph	**17a**	63
4	Hexane-ether (5:1)	PhCHO	CH(OH)Ph	**17a**	82
5	Hexane-ether (10:1)	PhCHO	CH(OH)Ph	**17a**	90
6	Hexane-ether (10:1)	MeOH	H	**16**	74
7	Hexane-ether (10:1)	CD_3OD	D	**17b**	73
8	Hexane-ether (10:1)	$H_2C{=}CHCH_2Br$	$CH_2CH{=}CH_2$	**17c**	58
9	Hexane-ether (10:1)	$Ph_2C{=}O$	$C(OH)Ph_2$	**17d**	81
10	Hexane-ether (10:1)	$H_2C{=}CHCHO$	$CH(OH)CH{=}CH_2$	**17e**	71
11	Hexane-ether (10:1)	^{t}BuCHO	$CH(OH)Bu^{t}$	**17f**	52
12	Hexane-ether (10:1)	^{i}PrCHO	$CH(OH)Pr^{i}$	**17g**	44
13	Hexane-ether (10:1)	MeCHO	CH(OH)Me	**17h**	68

[a]Me_4Sn added at -78 °C before warming to 0 °C; [b]Pyrrolidine **16**, E=H was also obtained (50%).

When the organolithium was trapped with ethyl chloroformate, the ester **18** was isolated, in which the *N*-benzyl group had been replaced by the *N*-CO_2Et group. Hydrolysis of the ester-carbamate **18** with hydrochloric acid[23] gave the carboxylate **19**, a known GABA uptake inhibitor.[24] This synthesis of inhibitor **19** is accomplished in just four steps from commercially available 4-bromobut-1-ene.



8, R=Bu **18** **19**

We have shown that anionic cyclizations provide an efficient method for the preparation of a variety of 3-substituted pyrrolidines. The use of the trimethylstannane **8**, R=Me gives rise to the pyrrolidine **9**, R=Me, in which the trimethyltin group is reincorporated into the product and the cyclization can be conducted with less than one equivalent of methyllithium. In contrast, the use of the tributylstannane **8**, R=Bu allows the preparation of a variety of 3-substituted pyrrolidines **17**, by quench of the intermediate organolithium species **11**. We are currently investigating the stereoselectivity of this anionic cyclization and its application to the preparation of a range of cyclic amine products.

EXPERIMENTAL

All experiments involving organolithiums were carried out under an inert atmosphere of argon or nitrogen. Diethyl ether and THF were distilled from sodium benzophenone ketyl. Hexane was distilled from sodium hydride. Infrared spectra were recorded on a Perkin Elmer 881 spectrophotometer, using a polystyrene reference (1602 cm^{-1}). ^1H nuclear magnetic resonance (NMR) spectra were run on a Brucker AM250 (250 MHz), AM300 (300 MHz) or AM400 (400 MHz) instrument. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the reference. ^{13}C NMR were run on a Brucker AM250 (62.9 MHz) or AM300 (75.5 MHz) instrument, with $CDCl_3$ (δ 77.2 ppm) as the reference. Mass spectra were run on a Kratos Profile instrument.

Preparation of the stannanes 8

N-*Benzyl*–N-*but*-3-*enyl-aminomethyltributyltin* **8**, R=Bu

To *N*-benzyl–*N*-but-*3*-enylamine (0.50 g, 3.13 mmol) and K_2CO_3 (0.86 g, 6.21 mmol) in dry MeCN (5 cm^3) under nitrogen at room temperature was added iodomethyltri–*n*-butyltin[11] (1.44 g, 3.34 mmol). After 4 d saturated $NaHCO_3$ (20 cm^3) was added and the mixture was extracted with CH_2Cl_2 (3 x 25 cm^3). The combined organic layers were dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate to give the *stannane* **8**, R=Bu (0.88 g, 61%)[12] as an oil, R_f [light petroleum (40-60°C)-ethyl acetate (1:5)] 0.76, $\nu_{max.}$ (oil) 1641 cm^{-1} (C=C); δ_H ($CDCl_3$) 7.39-7.18 (5H, m, C_6H_5), 5.80 (1H, ddt, *J* 16.5, 10.0 and 7.0 Hz, CH_2=C*H*), 5.04 (1H, d, *J* 16.5 Hz, CH_AH_B=CH), 4.99 (1H, d, *J* 10.0 Hz, CH_AH_B=CH), 3.47 (2H, s, CH_2Ph), 2.64 (2H, s, CH_2Sn), 2.41 (2H, t, *J* 7.0 Hz, CH_2CH_2N), 2.26 (2H, q, *J* 7.0 Hz, CH_2CH_2N), 1.64-1.17 {18H, m, $[(CH_2)_3CH_3]_3$} and 0.91 {9H, t, *J* 7.0 Hz, $[(CH_2)_3CH_3]_3$}; δ_C ($CDCl_3$) 139.92, 136.87, 128.73, 128.12, 126.75, 115.30, 62.81, 57.49, 42.83, 32.03,

29.23, 27.43, 10.22 and 8.35; (Found M^+, 465.2429. $C_{24}H_{43}NSn$ requires M, 465.2418); *m/z* 424 (1%, M - CH_2=$CHCH_2$), 174 [100, M - $(C_4H_9)_3Sn$] 91 (76, CH_2Ph) and 55 (6, CH_2=$CHCH_2CH_2$).

N-*Benzyl*–N-*but*–3-*enyl-aminomethyltrimethyltin* **8**, R=Me

In the same way as stannane **8**, R=Bu, *N*-benzyl–*N*-but-*3*-enylamine (1.03 g, 6.37 mmol) and iodomethyltrimethyltin[11] (2.04 g, 6.69 mmol) in dry acetone gave the *stannane* **8**, R=Me (1.20 g, 56%) as an oil, R_f [hexane-ethyl acetate (2:1)] 0.59; $\nu_{max.}$ (oil) 1641 (C=C) and 1495 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.39-7.21 (5H, m, C_6H_5), 5.83 (1H, ddt, *J* 17.0, 10.0 and 7.0 Hz, CH_2=C*H*), 5.05 (1H, d, *J* 17.0 Hz, CH_AH_B=CH), 5.02 (1H, d, *J* 10.0 Hz, CH_AH_B=CH), 3.47 (2H, s, CH_2Ph), 2.67 (2H, s, CH_2Sn), 2.47 (2H, t, *J* 7.0 Hz, CH_2CH_2N), 2.29 (2H, q, *J* 7.0 Hz, CH_2CH_2N) and 0.20 [9H, s, $Sn(CH_3)_3$]; δ_C ($CDCl_3$) 136.83, 139.76, 128.76, 128.18, 126.83, 115.40, 62.54, 57.38, 44.29, 31.99 and -8.45; (Found: M^+, 339.1015. $C_{15}H_{25}NSn$ requires M, 339.1008); *m/z* 298 (4%, M - CH_2=$CHCH_2$), 174 [100, M - $(CH_3)_3Sn$], 135 (46, CH_3SnH), 91 (86, CH_2Ph) and 55 (54, CH_2=$CHCH_2CH_2$).

Cyclization of the stannane 8, R=Me

Using stoichiometric methyllithium:

To stannane **8**, R=Me (0.23 g, 0.68 mmol) in dry THF (2 cm^3) under nitrogen at -78 °C was added methyllithium (1.38 mol dm^{-3} in Et_2O, 0.50 cm^3, 0.69 mmol). After 0.5 h the mixture was warmed to 0 °C and stirred for 0.5 h before quenching with water (10 cm^3). The mixture was extracted with Et_2O (3 x 10 cm^3), dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (99:1 to 50:50) to give the *pyrrolidine* **9**, R=Me as an oil (127 mg, 55%), R_f [hexane-ethyl acetate (7:3)] 0.27; $\nu_{max.}$ (oil) 1606 and 1496 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.36-7.21 (5H, m, C_6H_5), 3.59 (2H, ABq, *J* 13 Hz, CH_2Ph), 2.84 (1H, dd, *J* 8.5 and 7.0 Hz $NCH_AH_BCHCH_2Sn$), 2.73-2.64 (1H, m, $NCH_CH_DCH_2$), 2.50-2.37 [2H, m, $CH(CH_2Sn)$ and $NCH_CH_DCH_2$), 2.20-2.11 (1H, m, $NCH_2CH_EH_F$), 2.01 (1H, dd, *J* 8.5 and 7.5 Hz, $NCH_AH_BCHCH_2Sn$), 1.31 (1H, dtd, *J* 12.5, 9.0 and 6.0 Hz, $NCH_2CH_EH_F$), 0.97 (2H, d, *J* 7.5 Hz, CH_2Sn) and 0.06 [9H, s, $Sn(CH_3)_3$]; δ_C ($CDCl_3$) 139.32, 128.87, 128.15, 126.80, 64.15, 60.84, 54.06, 36.05, 34.47, 18.37 and -9.67; (Found: M^+ - CH_3, 324.0786. $C_{14}H_{22}NSn$ requires M - CH_3, 324.0774); *m/z* 324 (33%, M^+ - CH_3), 174 [97, M - $(CH_3)_3Sn$] and 91 (100, CH_2Ph).

Using catalytic methyllithium:

In the same way as stoichiometric methyllithium, methyllithium (1.18 mol dm^{-3} in Et_2O, 0.81 cm^3, 0.94 mmol) was added to the stannane **8**, R=Me (1.61 g, 4.76 mmol) in dry THF (16 cm^3) under argon at -78 °C. After 10 min at -78 °C, tetramethyltin (0.66 cm^3, 4.76 mmol) was added and the mixture was stirred for 10 min before being warmed to room temperature over 20 min. After 30 min, the mixture was re-cooled to -78 °C and quenched with MeOH (5 cm^3) to give, after purification as above, the pyrrolidine **9**, R=Me (1.12 g, 70%), data as above.

Removal of the trimethyltin group from 9, R=Me

N-*Benzyl*-3-*(*1', 1'-*dimethoxymethyl)pyrrolidine* **15**

To the pyrrolidine **9**, R=Me (0.1 g, 0.3 mmol) in dry Et_2O (2 cm^3) under argon at room temperature was added ethereal HCl solution (1.0 M). The Et_2O was removed *in vacuo* and dry MeOH (5 cm^3) was added. Ceric ammonium nitrate (0.81 g, 1.48 mmol) and a few crystals of *p*-toluenesulfonic acid were added portionwise. After 5 d the mixture was poured into CH_2Cl_2 (20 cm^3) and the organic phase was washed with water (2 x 20

cm^3) and saturated potassium bicarbonate solution (20 cm^3). The combined aqueous phases were extracted with CH_2Cl_2 (2 x 40 cm^3), the combined organic layers were dried ($MgSO_4$), evaporated and purified by column chromatography on silia gel, eluting with CH_2Cl_2-ethanol (99:1 to 90:10) to give the *pyrrolidine* **15** (42 mg, 61%) as an oil, R_f [CH_2Cl_2-ethanol (9:1)] 0.41; $\nu_{max.}$ (oil) 1604 and 1494 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.44-7.17 (5H, m, C_6H_5), 4.24 [1H, d, *J* 8.0 Hz, C*H*(OMe)$_2$], 3.61 (2H, ABq, *J* 12.0Hz, CH_2Ph), 3.34 (3H, s, OMe), 3.30 (3H, s, OMe), 2.69 (1H, dd, *J* 9.0 and 8.0 Hz, NCH_AH_BCHCH_2), 2.65-2.45 (3H, m, NCH_2CH_2 and NCH_2C*H*CH_2), 2.37 (1H, dd, *J* 9.0 and 6.4 Hz, NC$H_A$$H_BCHCH_2$), 2.00-1.86 (1H, m, C$H_2CH_A$$H_B$) and 1.73-1.60 (1H, m, CH_2C$H_A$$H_B$); δ_C ($CDCl_3$) 138.98, 128.07, 128.22, 126.92, 107.14, 60.46, 56.01, 53.96, 53.07, 52.82, 39.84 and 26.31; (Found: M^+, 235.1565. $C_{14}H_{21}NO_2$ requires *M*, 235.1572); *m/z* 235 (10 %, M^+), 220 (15, *M* - CH_3), 205 (38, *M* - 2 x CH_3), 188 (34, *M* - C_2H_6O), 91 (100, CH_2Ph) and 75 [25, $CH(OMe)_2$].

Cyclization of the stannane 8, R=Bu

General procedure:

n-Butyllithium (0.44 cm^3, 0.64 mmol, 1.48 mol dm^{-3} in hexanes) was added dropwise to the stannane **8**, R=Bu (0.16 g, 0.34 mmol) in dry hexane-Et_2O (2 cm^3, 10:1) at -78 °C under argon. After 10 min the mixture was warmed to room temperature over 30 min and was left to stand at room temperature for 2 h. The mixture was cooled to -78 °C and was quenched with dropwise addition of the electrophile (3.20 mmol). After warming to room temperature, the solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with CH_2Cl_2-EtOH-NH_3 (200:3:2) to give the pyrrolidine **17**.

N-Benzyl-3-methylpyrrolidine **16** (quench with methanol, 74%)[25]

R_f [hexane-ethyl acetate (7:1)] 0.09; $\nu_{max.}$ (oil) 3065 (=C-H), 1604 and 1495 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.43-7.18 (5H, m, C_6H_5), 3.62 (2H, ABq, *J* 12.8 Hz, CH_2Ph), 2.83 (1H, dd, *J* 9.0 and 7.5 Hz, NC$H_A$$H_BCHCH_3$), 2.71 (1H, ddd, *J* 9.0, 7.9 and 5.7 Hz, NC$H_C$$H_DCH_2$), 2.47 (1H td, *J* 9.0 and 6.4 Hz, NC$H_C$$H_DCH_2$), 2.26 [1H, ddqdd, *J* 12.0, 8.4, 7.5, 7.3 and 6.2 Hz, C*H*(CH_3)], 2.04 (1H, dtd, *J* 12.0, 9.0 and 6.2 Hz, NCH_2C$H_E$$H_F$), 2.01 (1H, dd, *J* 9.0 and 7.3 Hz, NC$H_A$$H_BCHCH_3$), 1.35 (1H, dtd, *J* 12.0, 9.0 and 6.2 Hz, NCH_2C$H_E$$H_F$) and 1.03 (3H, d, *J* 6.7 Hz, CHCH_3); δ_C ($CDCl_3$) 139.37, 128.55, 128.16, 126.81, 62.13, 60.80, 54.10, 32.65, 31.88 and 20.37; (Found: M^+, 175.1360. $C_{12}H_{17}N$ requires *M*, 175.1361); *m/z* 160 (2%, *M* - CH_3), 91 (100, CH_2Ph) and 84 (21, *M* - CH_2Ph).

N-*Benzyl*-3-*[1'-(2'-hydroxy-2'-phenyl)ethyl]pyrrolidine* **17a** (quench with benzaldehyde, 90%), ratio of diastereomers 1:1

R_f [CH_2Cl_2-EtOH-NH_3 (100:8:1)] 0.45; $\nu_{max.}$ (oil) 3362 (O-H), 1602 and 1493 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.44-7.15 [10H, m, $CH_2C_6H_5$ and CH(OH)C_6H_5], 4.72 (0.5H, dd, *J* 9.1 and 4.4 Hz, C*H*OH), 4.66 (0.5H, dd, *J* 8.2 and 5.3 Hz, C*H*'OH'), 3.95 (1H, broad s, CHO*H*), 3.71 (1H, ABq, *J* 12.6 Hz, CH_2Ph), 3.68 (1H, ABq, *J* 12.6 Hz, CH'$_2$Ph'), 2.88-2.68 (1H, m, NC$H_A$$H_BCHCH_2$), 2.71-2.58 (2H, m, NC$H_2CH_2$), 2.53-2.30 (2H, m, NC$H_A$$H_B$C*H*C$H_2$), 2.12-1.93 (1H, m, NC$H_2CH_C$$H_D$), 1.91-1.64 (2.5H, m, C$H_2$CHOH and NC$H_2CH_C$*H*$_D$) and 1.59-1.44 (0.5H, m, NCH_2CH$_C$*H*'$_D$); δ_C ($CDCl_3$) 145.12, 144.95, 137.53, 137.13, 129.21, 129.11, 128.64, 128.47, 128.45, 128.33, 127.53, 127.45, 127.41, 127.20, 125.89, 125.80, 73.22, 71.74, 60.22, 60.21, 59.68, 59.67, 53.38, 53.33, 44.75, 44.55, 34.60, 34.46, 30.79 and 28.59; (Found: M^+, 281.1786. $C_{19}H_{23}NO$ requires *M*, 281.1780); *m/z* 281 (12%, M^+), 190 (5, *M* - CH_2Ph), 159 (14, *M* - C_8H_8O), 120 (80, C_8H_8O) and 91 (100, CH_2Ph).

N-*Benzyl*-3-*(deuteriomethyl)pyrrolidine* **17b** (quench with CD_3OD, 73%)
R_f [hexane-ethyl acetate (1:1)] 0.09; $\nu_{max.}$ (oil) 3066 (=C-H), 1604 and 1495 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.39-7.20 (5H, m, C_6H_5), 3.62 (2H, ABq, *J* 12.0 Hz, CH_2Ph), 2.83 [1H, dd, *J* 8.7 and 7.5 Hz, $NCH_AH_BCH(CH_2D)$], 2.71 (1H, ddd, *J* 9.0, 8.0 and 5.5 Hz, $NCH_CH_DCH_2$), 2.48 (1H ddd, *J* 9.0, 8.0 and 5.5 Hz $NCH_CH_DCH_2$), 2.26 [1H, broad m, $CH(CH_2D)$], 2.12-1.96 [2H, m, $NCH_2CH_EH_F$ and $NCH_AH_BCH(CH_2D)$], 1.35 (1H, dddd, *J* 12.0, 8.0, 6.0 and 5.5 Hz, $NCH_2CH_EH_F$) and 1.02 (2H, m, $CHCH_2D$); δ_C ($CDCl_3$) 139.57, 128.91, 128.25, 126.88, 62.22, 60.84, 54.14, 32.71, 31.87 and 20.08 (t, *J* 9.6 Hz, CH_2D); (Found: M^+, 176.1424. $C_{12}H_{16}DN$ requires *M*, 176.1425); *m/z* 176 (17%, M^+), 91 (64, CH_2Ph), 84 (18, *M* - CH_2Ph) and 55 (100, C_4H_7).

N-*Benzyl*-3-*[1'-(but-3'-enyl)]pyrrolidine* **17c** (quench with allyl bromide, 58%)
R_f [hexane-ethyl acetate (1:1)] 0.20; $\nu_{max.}$ (oil) 3066 (=C-H), 1604 and 1494 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.39-7.18 (5H, m, C_6H_5), 5.81 (1H, ddt, *J* 17.0, 10.5 and 6.5 Hz, $CH_2=CH$), 5.00 (1H, dq, *J* 18.0 and 2.0 Hz, $CH_AH_B=CH$), 4.94 (1H, d, *J* 10.0 Hz, $CH_AH_B=CH$), 3.61 (2H, ABq, *J* 12.0 Hz, CH_2Ph), 2.83 (1H, dd, *J* 8.5 and 7.5 Hz, $NCH_CH_DCHCH_2$), 2.71 (1H, ddd, *J* 9.0, 7.9 and 5.5 Hz, $NCH_EH_FCH_2$), 2.44 (1H td, *J* 9.0 and 6.5, $NCH_EH_FCH_2$), 2.26-2.10 (1H, m, $CHCH_2$), 2.10-1.94 (4H, m, $NCH_CH_DCHCH_2$, $NCH_2CH_GH_H$ and $CH_2=CHCH_2$), 1.47 (2H, q, *J* 7.5 Hz, $CH_2=CHCH_2CH_2$) and 1.50-1.35 (1H, m, $NCH_2CH_GH_H$); δ_C ($CDCl_3$) 139.37, 138.75, 128.81, 128.17, 126.81, 114.33, 60.82, 60.49, 53.92, 37.08, 34.95, 32.54 and 30.77; (Found: M^+, 215.1672. $C_{15}H_{21}N$ requires *M*, 215.1674); *m/z* 215 (19%, M^+), 174 (13, *M* - C_3H_5), 138 (9, *M* - C_6H_5) and 91, (100, CH_2Ph).

N-*Benzyl*-3-*[1'-(2'-hydroxy-2',2'-diphenyl)ethyl]pyrrolidine* **17d** (quench with benzophenone, 82%)
R_f [$CHCl_3$-MeOH (20:1)] 0.27; $\nu_{max.}$ (oil) 3340 (O-H), 1600 and 1490 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.55-7.25 (15H, m, 3xPh) 3.61 (2H, ABq, *J* 15.0 Hz, CH_2Ph), 2.69 (1H, dd, *J* 8.0 and 6.0 Hz, $NCH_AH_BCHCH_2$), 2.60-2.50 (2H, m, NCH_2CH_2), 2.46 [2H, dd, *J* 5.5 and 1.5 Hz, $CH_2C(OH)$], 2.36-2.23 (2H, m, $NCH_AH_BCHCH_2$ and $NCH_AH_BCHCH_2$), 1.92-1.81 (1H, m, $NCH_2CH_CH_D$) and 1.52-1.41 (1H, m, $NCH_2CH_CH_D$); δ_C ($CDCl_3$) 147.64, 147.37, 137.46, 129.24, 128.36, 128.11, 127.35, 126.79, 126.73, 126.06, 126.04, 78.01, 60.57, 60.21, 53.13, 46.87, 33.56 and 31.70; (Found: M^+, 357.2076. $C_{25}H_{27}NO$ requires *M*, 357.2092); *m/z* 357 (3%, M^+), 174 [15, *M* - $C(OH)Ph_2$], 159 [79, *M* - $CH_2C(OH)Ph_2$] and 91 (100, CH_2Ph).

N-*Benzyl*-3-*[1'-(2'-hydroxy-but-3'-enyl)]pyrrolidine* **17e** (quench with acrolein, 65%), ratio of diastereomers 1:1
R_f [CH_2Cl_2-EtOH-NH_3 (100:8:1)] 0.32 and 0.23; $\nu_{max.}$ (oil) 3370 (O-H), 1640 (C=C), 1605 and 1495 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.39-7.20 (5H, m, C_6H_5), 5.95-5.78 (1H, m, $CH=CH_2$), 5.28-5.03 (2H, m, $CH=CH_2$), 4.23-4.04 (1H, m, CHOH), 3.62 (2H, ABq, *J* 12.5 Hz, CH_2Ph), 3.61 (2H, ABq, *J* 13.0 Hz, CH'_2Ph), 2.85-2.71 (1H, m, $NCH_AH_BCHCH_2$), 2.64-2.22 (3H, m, $NCH_AH_BCHCH_2$ and NCH_2CH_2), 2.15-1.93 (1.5H, m, $NCH_2CH_CH_D$ and $NCH'_2CH''_2$) and 1.71-1.43 (2.5H, m, CH_2CHOH and $NCH_2CH_CH_D$); (Found: M^+, 231.1628. $C_{15}H_{21}NO$ requires *M*, 231.1623); *m/z* 214 (2%, *M* - OH), 174 [10, *M* - $CH(OH)CH=CH_2$], 160 (10, *M* - $CH_2CH(OH)CH=CH_2$] and 91 (100, CH_2Ph).

N-*Benzyl-3-[1'-(2'-hydroxy-3',3'-dimethylbutyl)]pyrrolidine* **17f** (quench with pivalaldehyde, 52%), ratio of diastereomers 1:1

R_f [hexane-ethyl acetate (1:1)] 0.02; $\nu_{max.}$ (oil) 3408 (O-H), 1604 and 1494 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.40-7.18 (5H, m, C_6H_5), 3.74-3.57 (2H, m, CH_2Ph), 3.22 (0.5H, t, *J* 11.0 Hz, C*H*OH), 3.21 (0.5H, t, *J* 11.0 Hz, C*H'*OH'), 2.91 (1H, broad s, CHO*H*), 2.90-2.28 (5H, m, CH_2NCH_2CH), 2.15-1.97 (1H, m, NCH_2CHCH_2), 1.65-1.32 (3H, m, NCH_2CH and CH_2CHOH) and 0.80 [9H, s, $C(CH_3)_3$]; δ_C ($CDCl_3$) 133.05, 132.81, 123.84, 123.76, 123.10, 122.00, 121.91, 73.16, 72.16, 55.20, 55.14, 55.06, 54.82, 48.40, 48.35, 31.63, 31.59, 29.62, 29.60, 29.52, 29.46, 25.33, 24.50, 20.63 and 20.46; (Found: 261.2097 $C_{17}H_{27}NO$ requires *M*, 261.2092); *m/z* 261 (26%, M^+), 204 (3, *M* - C_4H_9), 120 (100, $C_8H_{10}N$) and 91 (62, CH_2Ph).

N-*Benzyl-3-[1'-(2'-hydroxy-3'-methylbutyl)]pyrrolidine* **17g** (quench with isobutyraldehyde, 44%), ratio of diastereomers 1:1

R_f [CH_2Cl_2-EtOH-NH_3 (100:8:1)] 0.25 and 0.22; $\nu_{max.}$ (oil) 3381 (O-H), 1604 and 1495 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.47-7.20 (5H, m, C_6H_5), 3.79-3.55 (2H, m, CH_2Ph), 3.46-3.33 (1H, m, C*H*OH), 2.98 (1H, broad s, CHO*H*), 2.92-2.30 (4H, m, CH_2NCH_2), 2.16-1.98 (2H, m, $NCH_2CHCH_AH_B$), 1.79-1.20 (3H, m, $NCH_2CHCH_AH_B$ and CH_2CHOH), 1.19-1.07 [1H, m, $CH(CH_3)_2$] and 0.92 [6H, d, *J* 6.6 Hz, $CH(CH_3)_2$]; δ_C ($CDCl_3$) 132.87, 123.80, 123.11, 121.99, 70.00, 68.59, 55.19, 55.13, 55.08, 54.88, 48.38, 48.24, 34.19, 33.81, 29.24, 28.74, 28.66, 25.51, 23.76, 13.51, 12.52 and 12.02; (Found: M^+, 247.1933. $C_{16}H_{25}NO$ requires *M*, 247.1936); *m/z* 204 (2%, *M* - C_3H_7), 156 (4, *M* - CH_2Ph) and 91 (100, CH_2Ph).

N-*Benzyl-3-[1'-(2'-hydroxypropyl)]pyrrolidine* **17h** (quench with acetaldehyde, 68%), ratio of diastereomers (unassigned) 2:1

R_f [hexane-ethyl acetate (1:1)] 0.02; $\nu_{max.}$ (oil) 3371 (O-H), 1604 and 1495 cm^{-1} (Ph); δ_H ($CDCl_3$) 7.41-7.13 (5H, m, C_6H_5), 4.20-3.62 (3H, m, CH_2Ph and C*H*OH), 2.82-2.52 (3H, m, $CHNCH_2$), 2.43-2.24 (2H, m, C*H*NCH_2CH), 2.07-1.93 (1H, m, $NCH_2CH_AH_B$), 1.72-1.61 (0.67H, m, $NCH_2CH_AH_B$), 1.55-1.48 (1H, m, CH_CH_DCHOH) and 1.34-1.15 (4.33H, m, $NCH_2CH_AH'_B$, CH_CH_DCHOH and CH_3); δ_C ($CDCl_3$) 138.43, 138.30, 128.97, 128.80, 128.32, 128.30, 128.02, 127.22, 66.58, 64.64, 60.46, 60.15, 59.84, 57.94, 53.67, 53.56, 44.75, 44.35, 38.87, 34.20, 30.92, 26.96, 23.82 and 23.60; (Found: M^+, 219.1623. $C_{14}H_{21}NO$ requires *M*, 219.1623); *m/z* 204 (1%, *M* - CH_3), 174 (2, *M* - CH_3CHOH), 128 (4, *M* - CH_2Ph) and 91 (100, CH_2Ph).

*Ethyl [3-(*N-*Ethoxycarbonyl-pyrrolidine)]ethanoate* **18** (quench with ethyl chloroformate, 68%)

R_f [hexane-ethyl acetate (1:1)] 0.15; $\nu_{max.}$ (oil) 1735 (C=O) and 1702 cm^{-1} (C=O), δ_H ($CDCl_3$) 4.15-4.06 (4H, m, $NCO_2CH_2CH_3$ and $CH_2CO_2CH_2CH_3$), 3.66-3.56 (1H, br m, $NCH_AH_BCHCH_2$), 3.53-3.39 (1H, br m, $NCH_CH_DCH_2$), 3.36-3.25 (1H, br m, $NCH_CH_DCH_2$), 3.02-2.91 (1H, br m, $NCH_AH_BCHCH_2$), 2.60-2.50 (1H, br m, $CHCH_2CO_2Et$), 2.38-2.33 (2H, m, CH_2CO_2Et), 2.10-2.00 (1H, br m, $NCH_2CH_EH_F$), 1.60-1.47 (1H, br m, $NCH_2CH_EH_F$) and 1.26-1.18 (6H, m, $NCO_2CH_2CH_3$ and $CH_2CO_2CH_2CH_3$); δ_C ($CDCl_3$) 171.99, 155.09, 60.87, 60.48, 51.18, 50.89, 45.40, 45.09, 37.60, 35.30, 34.49, 31.47, 30.76, 14.78 and 14.17, (Found: M^+, 229.1308. $C_{11}H_{19}NO_4$ requires *M*, 229.1314), *m/z* 229 (15 %, M^+), 200 (11, *M* - C_2H_5), 184 (44, *M* - OC_2H_5), 156 (66, *M* - $CO_2C_2H_5$) and 141 (100, *MH* - $CH_2CO_2C_2H_5$).

3-pyrrolidine ethanoic acid **19**[23,24] (71%)

Carbamate **18** (60 mg, 0.26 mmol) in 6M hydrochloric acid, (2.0 cm^3, 12.0 mmol) was heated under reflux for 4 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in water (3.0 cm^3). The aqueous solution was purified on an Amberlite® 420-OH-packed column, eluting with water (100 cm^3) followed by aqueous acetic acid (100 cm^3, 10 % v/v). The acetic acid eluants were concentrated *in vacuo* to give the acid **19** (71%), spectroscopic data identical to literature.[23,24]

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