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A Radical Cyclisation Approach to Pyroglutamates

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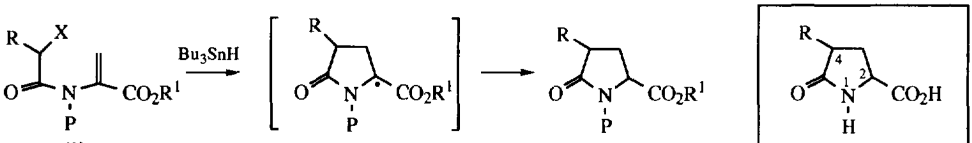
Abstract: Treatment of serine-derived *N*-(α-haloacetamido)dehydroalanine derivatives with tributyltin hydride in boiling benzene or toluene afforded pyroglutamates in 47-84% yield. The radical cyclisation reaction, which proceeded regioselectively in a disfavoured 5-*endo-trig* manner, was found to be most efficient when dichloro- and trichloroamides were employed as starting materials.

Pyroglutamic acid, a simple derivative of glutamic acid, has been widely used as a chiral building block for the synthesis of nitrogen containing natural products.[1] Recently the preparation of 4-substituted pyroglutamates (**1**) has attracted particular interest. These compounds which are important intermediates in natural product synthesis[1] can, for example, be hydrolysed to biologically important 4-substituted glutamic acid derivatives[2] or reduced to proline derivatives.[2b,3] The most common approach to (**1**) has centred on regioselective deprotonation of protected pyroglutamic acid at the C-4 position followed by quenching with an electrophile (*e.g.* alkyl halides,[4] aldehydes,[5] activated imines,[6] Bredereck's reagent,[7] or 2-toluenesulfonyl-3-phenyloxazilidine[8]). Thus, for example, Ezquerra and co-workers[4a] have reported that the *C*-alkylation of *N*-BOC protected ethyl pyroglutamate proceeds in good to excellent yield using a range of reactive electrophiles. In this paper[9] we wish to report full details of a new and flexible approach to pyroglutamates of type (**1**) which involves the 5-*endo-trig* radical cyclisation of an α-chloroamide.

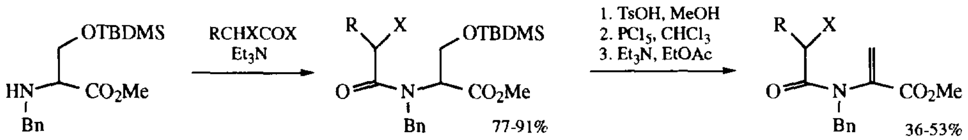


Scheme 1

Ikeda and co-workers[10] have recently demonstrated the ability of certain α-halogenated amides to undergo radical cyclisation in a 5-*endo-trig* process and we envisaged that the dehydroamino acid derivative (**2**) would react with tributyltin hydride *via* an *endo* cyclisation, to afford the protected pyroglutamate (**4**) regioselectively *via* the captodatively stabilised radical (**3**) (Scheme 1). This approach could allow the preparation of a variety of 4-substituted pyroglutamates (**1**), with a range of R substitutents.

(a) Preparation of Cyclisation Precursors

To test this methodology, initial studies concentrated on the synthesis of the dehydroamino acid precursors **(5)**-**(11)**. The dehydroamino acids **(6)**, **(8)** and **(9)** were prepared from the protected DL-serine derivative **(12)** as shown in Scheme 2. This involved treatment of **(12)** with the appropriate acid chloride or bromide to afford the amides **(13)**-**(15)**. On desilylation, primary alcohol chlorination and finally triethylamine mediated elimination, the desired dehydroamino acids **(6)**, **(8)** and **(9)** were isolated in reasonable yields. A more efficient synthesis was devised for **(5)**, **(10)** and **(11)** based on the reaction of the DL-serine derivative **(16)**[15] with two equivalents of the appropriate acid chloride as shown in Scheme 3.[11] The intermediate diester could be eliminated *in situ* (at room temperature) using Et_3N or DBU to afford **(5)** and **(10)** while more forcing conditions (DBU and heating) were required for the preparation of **(11)**. The remaining dehydroamino acid precursor **(7)** was prepared in excellent yield by Finkelstein reaction of chloride **(7)** using sodium iodide in acetone at room temperature (Scheme 4).

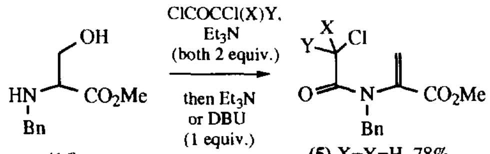


(12)

(13) R=H, X=Br
(14) R=Me, X=Cl
(15) R=Ph, X=Cl

(6) R=H, X=Br
(8) R=Me, X=Cl
(9) R=Ph, X=Cl

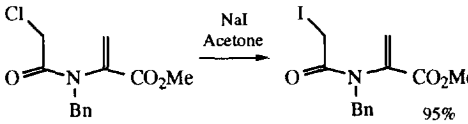
Scheme 2



(16)

(5) X=Y=H, 78%
(10) X=Cl, Y=H, 89%
(11) X=Y=Cl, 88%

Scheme 3



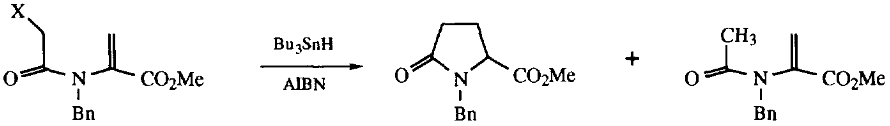
(5) **(7)**

Scheme 4

(b) Preliminary Cyclisation Studies

On treatment of α-chloroamide **(5)** with 1.1 equivalents of tributyltin hydride in boiling benzene the desired pyroglutamate **(17)** resulting from a 5-*endo-trig* cyclisation was isolated in 52% yield after column chromatography (Scheme 5). In addition, the dehydroalanine derivative **(18)** derived from simple chloroamide reduction was formed in a very low 8% yield. The cyclisation was regioselective and no β-lactam product **(19)**, resulting from a 4-*exo-trig* cyclisation, was isolated. It should be noted that in spite of the relatively low product isolation, no starting material **(5)** was recovered (or observed in the crude ^1H NMR spectrum). This was thought to be the result of competitive addition of the tributyltin radical to the double bond of **(5)**,[12] although no conclusive evidence for the formation of the expected adduct **(20)** could be obtained and polymerisation may be responsible. A similar result was obtained on reaction of the bromide **(6)** with tributyltin hydride (under the same conditions) and the pyroglutamate **(17)** and dehydroalanine **(18)** were isolated in 47% and 8% yields respectively. It was surprising to find that radical cyclisation of the more reactive iodide **(7)** afforded a lower yield (38%) of the desired pyroglutamate **(17)**.

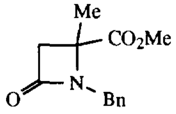
From these results it can be seen that the precursor chloride (**5**) afforded the most efficient cyclisation and as a result all subsequent cyclisation reactions made use of chloride precursors.



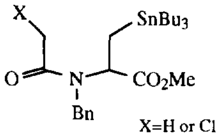
(**5**)-(**7**) (**17**) (**18**)

Halide	X	(17) Yield (%)	(18) Yield (%)
(5)	Cl	52	8
(6)	Br	47	8
(7)	I	38	7

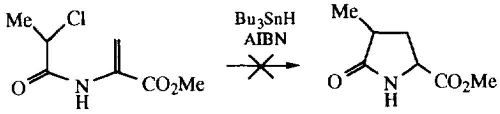
Scheme 5



(**19**)



(**20**)

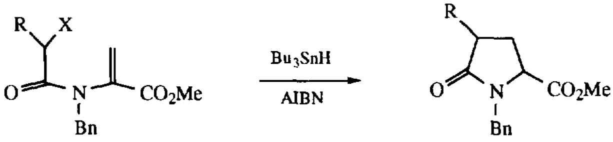


(**21**) (**22**)

Scheme 7

(c) Cyclisation of Substituted Chloroamides

The tin-mediated cyclisation reactions of 2-chloropropionamide (**8**) and 2-chloro-2-phenylacetamide (**9**) were then investigated (Scheme 6). On cyclisation of (**8**) in boiling benzene the 4-methylpyroglutamate (**23**) was formed in 47% yield. This was isolated as an inseparable mixture of *trans*-:*cis*- diastereomers in the approximate ratio 1.75:1 as indicated from the ^{1}H NMR spectrum.[4a] The *N*-benzyl substituent was found to be necessary for cyclisation; reaction of the corresponding N-H derivative (**21**) (with tributyltin hydride in boiling benzene or toluene) afforded no pyroglutamate (**22**) (Scheme 7). The 4-phenylpyroglutamate (**24**) was isolated in similar yield (52-56%) and diastereoselectivity (*trans*-:*cis*-, 1:2.1) from the the cyclisation of (**9**) in benzene or toluene (Scheme 6). No products resulting from the simple reduction of chloroamides (**8**)-(**9**) were apparently formed in these reactions.



(**8**), R=Me
(**9**), R=Ph

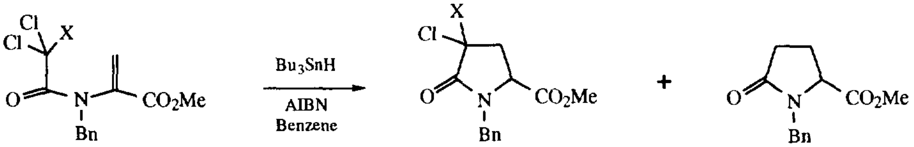
(**23**), R=Me
(**24**), R=Ph

Halide	Reaction Temp. (°C)	Product (yield %)	C-2:C-4 *trans-/cis-* ratio
(8)	80	(23) (47)	1.75:1
(9)	80	(24) (56)	1:2.1
(9)	110	(24) (52)	1:2.1

Scheme 6

(d) Cyclisation of Polychlorinated Precursors

More efficient pyroglutamate formation was realised on cyclisation of the dichloro- and trichloroamides **(10)** and **(11)** (Scheme 8). Thus on reaction of **(10)** with 1.1 equivalents of tributyltin hydride the desired 4-chloro derivative **(25)** was formed in 33% yield (with a *trans-*:*cis-* ratio of 3:1). In addition the unsubstituted pyroglutamate **(17)**, formed by tin hydride reduction of **(25)**, was isolated in 36% yield. When the reaction was carried out using 2.2 equivalents of tin hydride the yield of **(17)** increased to 70%. Cyclisation of the trichloride **(11)** using 1.1 and 3.3 equivalents of tin hydride was found to proceed extremely efficiently and the desired pyroglutamates **(26)** and **(17)** were isolated in excellent 81 and 84% yields respectively. The reaction using 1.1 equivalents of tin hydride also afforded a small amount (4%) of **(25)**. The efficient formation of **(17)** from **(10)**, and particularly from **(11)**, contrasted with the earlier cyclisation of the monochloroacetamide **(5)** (Scheme 5).



(10), X=H
(11), X=Cl

(25), X=H
(26), X=Cl

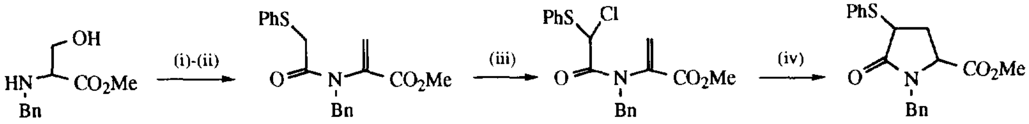
(17)

Halide	Equivalents of Bu_3SnH	Products (yield %)
(10)	1.1	**(25)** (33) + **(17)** (36)
(10)	2.2	**(17)** (70)
(11)	1.1	**(26)** (81) + **(25)** (4)
(11)	3.3	**(17)** (84)

Scheme 8

(e) Cyclisation of Sulfanyl Precursor

The cyclisation of the *S*-phenyl derivative **(28)** was then explored. This was prepared from **(16)** and involved *N*-acylation, mediated by BOP-Cl, followed by elimination using dichloroacetyl chloride to afford the dehydroamino acid derivative **(27)** as shown in Scheme 9. This was then chlorinated using *N*-chlorosuccinimide in carbon tetrachloride to afford the desired precursor **(28)**. On treatment of crude **(28)** with tributyltin hydride (1.1 equivalents) the pyrrolidinone **(29)** was isolated as a 2:1 mixture of diastereomers in only 28% yield. However, when the starting material **(28)** was purified prior to cyclisation (using column chromatography) although a similar diastereoselectivity (1.5:1) was observed, the yield of **(29)** was found to increase to 46%. It should also be noted that attempts to prepare the dichloro derivative of **(27)** by reaction with 2.2 equivalents of *N*-chlorosuccinimide were unsuccessful.

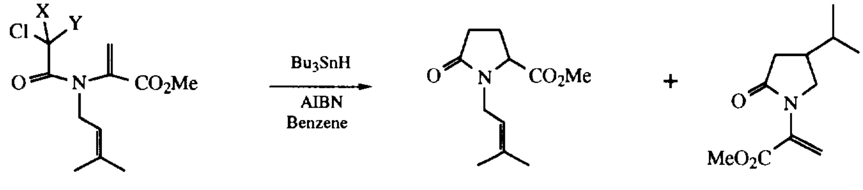


(16) **(27)** **(28)** **(29)**

(i) $PhSCH_2CO_2H$, BOP-Cl, Et_3N, CH_2Cl_2, 59%; (ii) $ClCOCHCl_2$, Et_3N, CH_2Cl_2, 85%; (iii) NCS, CCl_4, 70%; (iv) Bu_3SnH, AIBN, C_6H_6, 46%.

(f) 5-*Endo* versus 5-*Exo* Cyclisation

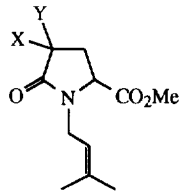
The successful 5-*endo-trig* cyclisation reactions described above, led us to examine the cyclisation of the *N*-(3-methyl-2-butenyl)enamides **(30a-c)** (Scheme 9). With these precursors a 5-*exo-trig* radical cyclisation to afford the pyrrolidinone **(32)** is possible and this is expected to be the predominant process.[13] On reaction of the chloroamide **(30a)** with tributyltin hydride, pyrrolidinone **(32)** was formed, but only in 12% yield, the major product (29%) being the 5-*endo-trig* cyclisation product **(31)** (entry i). A more pronounced 4:1 ratio of 5-*endo* **(31)**:5-*exo* **(32)** products was obtained on reaction of dichloroamide **(30b)** with 2.2 equivalents of tin hydride (entry ii); when 1.1 equivalents of tin hydride were used the chlorides **(33)** and **(35)** were isolated in 38% and 16% yields respectively. These results may be explained by the extra stability of the intermediate captodative[14] radical **(37)** produced on *endo* cyclisation over the corresponding tertiary radical **(38)** formed *via* the *exo* process. Reaction of the trichloroamide **(30c)** with 3.3 equivalents of tin hydride also gave predominantly the 5-*endo* product **(31)** (entry iii) while reaction with 1.1 equivalents (of tin hydride) afforded the dichloropyrrolidinones **(34)** and **(36)** in a 1:1 ratio. It is interesting to note that even though the dichloroamide radical intermediate derived from **(30c)** is very electrophilic, cyclisation on to the more electron poor double bond (of the dehydroamino acid) is still observed and the 5-*endo* product is isolated in 22-27% yield. Finally, the ^{1}H NMR spectrum of **(30b)** recorded at 80°C (d_8-toluene) clearly shows free rotation about the amide bond and thus the *endo*:*exo* product ratios observed are unlikely to be due to any conformational effect.



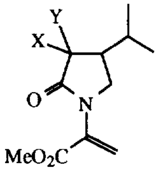
(30a-c) **(31)** **(32)**

ENTRY	(30)	X	Y	Equivalents of Bu_3SnH	Yield of (31) (%)	Yield of (32) (%)
i	a	H	H	1.1	29	12
ii	b	Cl	H	2.2	46	11
iii	c	Cl	Cl	3.3	27	12

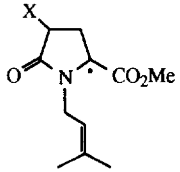
Scheme 9



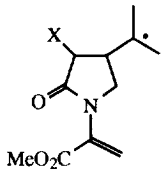
(33) X=Cl, Y=H
(34) X=Y=Cl



(35) X=Cl, Y=H
(36) X=Y=Cl



(37) X=H or Cl



(38) X=H or Cl

This work has demonstrated the utility of the 5-*endo-trig* cyclisation of chloroamides in pyroglutamate synthesis. Further studies directed towards the synthesis of chiral amino acids are currently underway.

Acknowledgements
We thank the EPSRC for a research studentship (K.G.) and Prof. R.J.K. Taylor for many helpful discussions.

Experimental

^1H NMR (δ^1H) and ^{13}C NMR ($\delta^{13}C$) spectra were recorded on a Jeol EX 270 spectrometer; the carbon spectra were recorded at 67.5 MHz and were assigned using DEPT experiments. Chemical shifts are reported in δ (ppm). Samples were prepared as solutions in $CDCl_3$ containing tetramethylsilane as internal standard or were referenced to an internal chloroform standard. Spectra which were complicated by the presence of conformers at room temperature were recorded in d_8-toluene at 80°C. Coupling constants (*J*) were recorded in Hertz (Hz) to the nearest 0.5 Hz. IR spectra (υ_{max}) were recorded on an ATI Mattison Genesis Series FT IR spectrometer as thin films. Mass spectra (MS) were recorded on a Fisons Instruments VG Analytical Autospec Spectrometer system. Thin layer chromatography (t.l.c.) was performed on Merck 5554 aluminium-backed silica gel plates. Compounds were visualized under a UV lamp, using alkaline potassium permanganate solution, ninhydrin or iodine. Column chromatography was carried out under gravity, using silica gel (Matrex Silica 60, 70-200 micron Fisons, or ICN flash silica 60, 32-63 microns). Commercially available reagents were used as supplied unless otherwise stated. Petroleum ether refers to the fraction of boiling range 40-60°C, which was redistilled before use. Tributyltin hydride was purchased from Lancaster Synthesis Ltd and distilled before use.

*Methyl (2R,S)-2-(*N*-benzylamino)-3-(*tert*-butyldimethylsiloxy)propanoate* (**12**)

The *N*-benzyl protected amino acid (**16**)[15] (3.00 g, 14.33 mmol) in dichloromethane (40 ml) was treated with triethylamine (2.20 ml, 15.76 mmol), *tert*-butyldimethylsilyl chloride (2.38 g, 15.76 mmol) and 4-dimethylaminopyridine (catalytic) and then allowed to stir overnight at room temperature. The reaction mixture was washed with water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford crude product. Column chromatography (silica; diethyl ether) afforded the silyl ether (**12**) (3.38 g, 73%) as a colourless oil; R_f 0.39 (petroleum ether-diethyl ether, 2:1); υ_{max} (thin film) 3351 (br), 1743 (vs), 1462 (s), 1388 (m), 1362 (m), 1253 (s), 1199 (s), 1108 (s), 1005 (w) and 836 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31-7.21 (5H, m, aromatics), 3.91-3.35 (8H, m, NC$\underline{H}$, C$\underline{H}_2$OSi, OC$\underline{H}_3$ and NC$\underline{H}_2$Ph), 1.98 (1H, br s, N$\underline{H}$), 0.84 (9H, s, SiC(C$\underline{H}_3$)$_3$) and 0.00 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (67.5 MHz, $CDCl_3$), 173.7 ($\underline{C}O_2CH_3$), 139.7 ($\underline{C}$=C), 128.3, 128.2, 126.9 ($\underline{C}$H=C), 64.5 ($\underline{C}H_2$OSi), 62.1 (N$\underline{C}$H), 51.9 ($\underline{C}H_2$Ph), 51.7 (O$\underline{C}H_3$), 25.6 (SiC($\underline{C}H_3$)$_3$), 18.8 (Si$\underline{C}$(CH$_3$)$_3$) and -5.5 (Si($\underline{C}H_3$)$_2$); *m/z* (CI, NH_3) 324 ($M+H^+$, 100%), 266 (20), 178 (10), 106 (10) and 91 (25); Found: $M+H^+$, 324.1988. $C_{17}H_{29}NO_3Si$ requires for $M+H^+$, 324.1994.

General Procedure for the Preparation of Silyl Amides (13), (14) and (15)

To a stirred solution of the amine (**12**) (3.84-9.29 mmol) in dry dichloromethane (20-50 ml) at 0°C was added triethylamine (4.22-10.22 mmol) followed by the dropwise addition of the acid halide (4.22-10.22 mmol) as a solution in dichloromethane (1-2 ml). After 0.5 h, the solution was gradually warmed to room temperature and washed with water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford the crude amide which was purified by column chromatography (silica) (77-91%).

*Methyl (2R,S)-2-(*N*-benzyl-2-bromoethanamido)-3-(*tert*-butyldimethylsiloxy)propanoate* (**13**)

Amine (**12**) (3.00 g, 9.29 mmol) was reacted with triethylamine (1.42 ml, 10.22 mmol) and 2-bromopropionyl bromide (0.89 ml, 10.22 mmol) following the general procedure. Column chromatography (silica; petroleum ether-diethyl ether, 1:1) afforded amide (**13**) (3.78 g, 89%) as a pale yellow oil; R_f 0.56 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 3415 (br), 2952 (m), 1743 (s), 1656 (s), 1461 (m), 1257 (m), 1205 (m), 1110 (m), 912 (w), 838 (m), 779 (m) and 730 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.43-7.29 (5H, m, aromatics), 4.96-4.70 and 4.24-3.87 (7H, m, $NC\underline{H}_2$, $NC\underline{H}$, $C\underline{H}_2Br$ and $C\underline{H}_2OSi$), 3.76 (3H, s, $OC\underline{H}_3$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$) and 0.00 (6H, s, $Si(C\underline{H}_3)_2$); δ_C (67.5 MHz, $CDCl_3$) 169.0, 168.3 ($N\underline{C}O$ and $\underline{C}O_2Me$), 136.5 ($\underline{C}$=CH), 128.8, 127.7, 126.3 ($\underline{C}$H=C), 61.5 ($\underline{C}H_2OSi$), 61.0 ($N\underline{C}H$), 52.7 ($\underline{C}H_2Ph$), 52.1 ($O\underline{C}H_3$), 26.1 ($\underline{C}H_2Br$), 25.6 ($SiC(\underline{C}H_3)_3$), 17.9 ($Si\underline{C}(CH_3)_3$) and -5.9 ($Si(\underline{C}H_3)_2$); *m/z* (CI, NH_3) 446 ($M^{81}+H^+$, 100%), 444 ($M^{79}+H^+$, 95), 388 (15), 366 (40), 332 (10) and 312 (15); Found: $M^{79}+H^+$, 444.1200. $C_{19}H_{30}BrNO_4Si$ requires for $M^{79}+H^+$, 444.1206.

*Methyl (2R,S)-2-(*N*-benzyl-2-chloropropanamido)-3-(*tert*-butyldimethylsiloxy)propanoate* (**14**)

This compound was prepared from the amine (**12**) (2.00 g, 6.20 mmol), triethylamine (0.95 ml, 6.81 mmol) and 2-chloropropionyl chloride (0.66 ml, 6.8 mmol) using the general procedure. Purification using column chromatography (silica; dichloromethane) afforded amide (**14**) (1.97 g, 77%) as a colourless oil; R_f 0.63 (dichloromethane); υ_{max} (thin film) 1739 (vs), 1652 (vs), 1450 (m), 1253 (m), 1197 (m), 838 (m) and 773 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.37-7.22 (5H, m, aromatics), 4.88-4.01 (6H, m, $CH_3C\underline{H}$, $C\underline{H}_2OSi$, $NC\underline{H}$ and $NC\underline{H}_2Ph$), 3.74 (3H, s, $OC\underline{H}_3$), 1.79 (3H, d, J =7, $C\underline{H}_3CH$), 0.81 (9H, s, $SiC(C\underline{H}_3)_3$) and 0.09 (6H, s, $Si(C\underline{H}_3)_2$); δ_C (67.5 MHz, $CDCl_3$) 170.9, 169.2 ($N\underline{C}O$ and $\underline{C}O_2Me$), 136.4 ($\underline{C}$=C), 128.7, 127.5, 126.0 ($\underline{C}$H=C), 61.6 ($\underline{C}H_2OSi$), 61.3 ($N\underline{C}H$), 52.2 ($O\underline{C}H_3$), 50.2 ($N\underline{C}H_2Ph$), 50.9 ($\underline{C}HCl$), 25.7 ($SiC(\underline{C}H_3)_3$), 21.2 ($\underline{C}H_3CH$), 18.1 ($Si\underline{C}(CH_3)_3$) and -5.8 ($Si(\underline{C}H_3)_2$); *m/z* (CI, NH_3) 416 ($M^{37}+H^+$, 35%), 414 ($M^{35}+H^+$, 100), 380 (15), 356 (40), 322 (15), 300 (45), 282 (40), 208 (25) and 91 (20): Found: $M^{35}+H^+$, 414.1867. $C_{20}H_{32}ClNO_4Si$ requires for $M^{35}+H^+$, 414.1865.

*Methyl (2R,S)-2-(*N*-benzyl-2-chloro-2-phenylethanamido)-3-(*tert*-butyldimethylsiloxy)propanoate* (**15**)

Amine (**12**) (1.24 g, 3.84 mmol) was reacted with triethylamine (0.59 ml, 4.22 mmol) and 2-chloro-2-phenylacetyl chloride (0.67 ml, 4.22 mmol) following the general procedure to afford, after column chromatography (silica; petroleum ether-diethyl ether, 2:1), the title compound (**15**) (1.66 g, 91%) as a colourless oil; R_f 0.31 (petroleum ether-diethyl ether, 2:1); υ_{max} (thin film) 1744 (vs), 1666 (vs), 1496 (m), 1361 (w), 1257 (m), 1174 (s), 1110 (m), 1006 (m), 910 (m), 837 (w), 779 (m), 732 (m) and 695 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$), 7.45-7.32 (10H, m, aromatics), 5.57 (1H, s, $PhC\underline{H}Cl$), 5.14-4.65 (3H, m, $NC\underline{H}$ and $NC\underline{H}_2Ph$), 4.32-4.09 (2H, m, $C\underline{H}_2OSi$), 3.83 (3H, s, $OC\underline{H}_3$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$) and 0.10 (6H, s, $Si(C\underline{H}_3)_2$); δ_C (67.5 MHz, $CDCl_3$), 169.1, 169.0 ($N\underline{C}O$, and $\underline{C}O_2CH_3$), 136.4, 135.8 (2 x $\underline{C}$=CH), 128.9, 128.7, 128.4, 128.1, 127.6, 126.5 ($\underline{C}$H=C), 61.7 ($\underline{C}H_2OSi$), 61.2 ($\underline{C}HClPh$), 56.4 ($N\underline{C}H$), 52.4 ($N\underline{C}H_2Ph$), 53.6 ($O\underline{C}H_3$), 25.6 ($SiC(\underline{C}H_3)_3$), 18.0 ($Si\underline{C}(CH_3)_3$) and -4.6 ($Si(\underline{C}H_3)_2$); *m/z* (CI, NH_3) 478 ($M^{37}+H^+$, 15%), 476 ($M^{35}+H^+$, 60), 442 (80), 384 (30), 310 (25), 106 (20) and 91 (100); Found: $M^{35}+H^+$, 476.2035. $C_{25}H_{34}ClNO_4Si$ requires for $M^{35}+H^+$, 476.2024.

General Procedure for the Preparation of Alkenes (6), (8) and (9)

p-Toluenesulfonic acid (catalytic) was added to a stirred solution of the silyl amide (**13**, **14** or **15**) (3.39-4.81 mmol) in methanol (20-40 ml) and stirred overnight. The methanol was removed *in vacuo*, the residue dissolved in ethyl acetate and washed with water, brine, dried (magnesium sulfate) and evaporated to afford crude alcohol which was purified by column chromatography (71-72%).

The alcohol (2.40-3.46 mmol) in chloroform (10-20 ml) was treated with phosphorus pentachloride (1.1 eq.) and stirred at room temperature for 12 h. The solution was washed with water, brine, dried (magnesium sulfate) and concentrated to afford the crude chloro- derivative. Triethylamine (1.1 eq.) was then added to a stirred solution of the chloro- derivative in ethyl acetate (20-40 ml) and elimination typically occurred within 12 h. The solution was washed with water, brine, dried (magnesium sulfate) and concentrated after which the alkene was purified by column chromatography (silica) to afford the desired alkene (**6**, **8** or **9**) as an oil (36-49%).

*Methyl 2-(*N*-benzyl-2-bromoethanamido)propenoate* (**6**)

Silyl amide (**13**) (1.50 g, 3.39 mmol) was reacted according to the general procedure above to give alkene (**6**) (0.38 g, 36%) as a pale yellow oil upon column chromatography (silica; diethyl ether); R_f 0.47 (diethyl ether); υ_{max} (thin film) 1726 (vs), 1670 (vs), 1633 (s), 1425 (m), 1350 (m), 1314 (w), 1087 (s), 981 (m), 802 (m) and 697 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.29-7.18 (5H, m, aromatics), 6.31 (1H, s, $C\underline{H}=C$), 5.50 (1H, s, $C\underline{H}=C$), 4.63 (2H, s, $NC\underline{H}_2Ph$), 3.72 (2H, s, $C\underline{H}_2Br$) and 3.71 (3H, s, $OC\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 166.2, 163.7 ($N\underline{C}O$ and $\underline{C}O_2CH_3$), 136.0 ($\underline{C}=CH_2$), 135.9 ($\underline{C}=CH$), 129.5, 128.7, 128.4 ($\underline{C}H=C$), 127.7 ($\underline{C}H_2=C$), 52.7 ($O\underline{C}H_3$), 51.1 ($N\underline{C}H_2Ph$) and 26.6 ($\underline{C}H_2Br$); *m/z* (CI, NH_3) 314 ($M^{81}+H^+$, 90%), 312 ($M^{79}+H^+$, 90), 268 (20), 232 (75), 190 (55), 175 (40) and 91 (100); Found: $M^{79}+H^+$, 312.0157. $C_{13}H_{14}BrNO_3$ requires for $M^{79}+H^+$, 312.0161.

*Methyl 2-(*N*-benzyl-2-chloropropanamido)propenoate* (**8**)

Following the general procedure amide (**14**) (2.00 g, 4.81 mmol) was reacted to afford, upon column chromatography (silica; petroleum ether-diethyl ether, 1:2), the alkene (**8**) (0.66 g, 49%) as a colourless oil; R_f 0.80 (petroleum ether-diethyl ether, 1:2); υ_{max} (thin film) 1732 (vs), 1674 (vs), 1633 (s), 1496 (m), 1407 (m), 1196 (s), 1063 (m), 980 (m), 729 (m) and 699 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.35-7.22 (5H, m, aromatics), 6.42 (1H, s, $C=C\underline{H}$), 5.61 (1H, s, $C=C\underline{H}$), 4.89 (1H, q, J =7, $CH_3C\underline{H}$), 4.33 (2H, s, $NC\underline{H}_2Ph$), 3.80 (3H, s, $OC\underline{H}_3$) and 1.68 (3H, d, J=7, $C\underline{H}_3CH$); δ_C (67.5 MHz, $CDCl_3$) 169.0, 164.0 ($N\underline{C}O$ and $\underline{C}O_2CH_3$), 136.2 ($\underline{C}=C$), 129.4, 128.9, 128.8, ($\underline{C}H=C$, $\underline{C}=CH_2$ and $C=\underline{C}H_2$), 52.8 ($O\underline{C}H_3$), 51.2 ($N\underline{C}H_2Ph$), 50.3 ($CH_3\underline{C}H$) and 20.9 ($\underline{C}H_3CH$): *m/z* (CI, NH_3) 300 ($M^{37}+NH_4^+$, 15%), 298 ($M^{35}+NH_4^+$, 45), 284 ($M^{37}+H^+$, 10), 282 ($M^{35}+H^+$, 30), 248 (100), 190 (25), 175 (15), 156 (40), 106 (25) and 91 (50); Found: $M^{35}+H^+$, 282.0897. $C_{14}H_{16}ClNO_3$ requires for $M^{35}+H^+$, 282.0905.

Methyl 2-(N-benzyl-2-chloro-2-phenylethanamido)propenoate (**9**)

Following the general procedure, amide (**15**) (1.70 g, 3.65 mmol) was reacted according to the general procedure to afford, after column chromatography (silica; diethyl ether), alkene (**9**) (0.67 g, 53%) as a colourless oil; R_f 0.63 (diethyl ether); υ_{max} (thin film) 1731 (vs), 1681 (vs), 1632 (s), 1455 (m), 1402 (w), 1382 (m), 1214 (m), 1196 (s), 1091 (m), 911 (m) and 697 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.56-7.12 (10H, m, aromatics), 6.32 (1H, s, C<u>H</u>=C), 5.50 (1H, s, C<u>H</u>=C), 5.34 (1H, s, PhC<u>H</u>Cl), 5.09-4.36 (2H, br s, $NC\underline{H}_2Ph$) and 3.60 (3H, s, $OC\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 167.2, 163.6 (N<u>C</u>O and $\underline{C}O_2CH_3$), 137.0 ($\underline{C}=CH_2$), 136.0, 135.8 (2 x <u>C</u>=CH), 130.3, 129.1, 128.7, 128.5, 128.3, 127.8 (<u>C</u>H=C), 128.1 ($\underline{C}H_2=C$), 57.8 (Ph<u>C</u>HCl), 52.7 ($N\underline{C}H_2Ph$) and 51.5 ($O\underline{C}H_3$); *m/z* (CI, NH_3) 346 ($M^{37}+H^+$, 35%), 344 ($M^{35}+H^+$, 100), 310 (60), 250 (10) and 91 (20); Found: $M^{35}+H^+$, 344.1056. $C_{19}H_{18}ClNO_3$ requires for $M^{35}+H^+$, 344.1053.

General 'One-Pot' Procedure for the Preparation of the Alkenes (5, 10 and 11)

To a stirred solution of the *N*-protected D,L-serine derivative (**16**)[15] (2.00-5.65 mmol) in dry dichloromethane (20-40 ml) at 0°C was added triethylamine followed by the dropwise addition of the desired acetyl chloride in dichloromethane (2-5 ml). The solution was allowed to warm to room temperature after 0.5 h and after an additional 1 h, t.l.c. indicated no starting material remained so triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene was added and the solution turned black as elimination occurred (1-96 h). The solution was then washed with 10% aq. citric acid, water, brine, dried (magnesium sulfate) and evaporated *in vacuo*. Column chromatography (silica) afforded the desired alkenes (**5, 10** and **11**) as pale yellow or colourless oils (78-89%).

Methyl 2-(N-benzyl-2-chloroethanamido)propenoate (**5**)

Following the general procedure chloroacetyl chloride (0.16 ml, 2.00 mmol) in dry dichloromethane (2 ml) was added to the serine derivative (**16**)[15] (0.19 g, 0.91 mmol) in dry dichloromethane (20 ml) containing triethylamine (0.28 ml, 2.00 mmol). No starting material remained by t.l.c. after 1 h so a further equivalent of triethylamine was added to effect elimination. Column chromatography (silica; petroleum ether-diethyl ether, 1:1) afforded the desired compound (**5**) (0.31 g, 78%) as a colourless oil; R_f 0.48 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 1725 (vs), 1676 (vs), 1633 (s), 1405 (m), 1323 (m), 1237 (w), 1090 (s), 976 (m), 857 (m) and 694 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.34-7.26 (5H, m, aromatics), 6.40 (1H, s, C<u>H</u>=C), 5.63 (1H, s, C<u>H</u>=C), 4.81 (2H, s, $NC\underline{H}_2Ph$), 4.09 (2H, s, $C\underline{H}_2Cl$) and 3.82 (3H, s, $OC\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 165.9, 163.4 (N<u>C</u>O and $\underline{C}O_2CH_3$), 136.6 ($\underline{C}=CH_2$), 135.8 (<u>C</u>=C), 129.5 ($\underline{C}H_2=C$), 128.7, 128.3, 127.6 (<u>C</u>H=C), 52.6 ($O\underline{C}H_3$), 51.1 ($N\underline{C}H_2Ph$) and 41.3 ($\underline{C}H_2Cl$); *m/z* (CI, NH_3) 270 ($M^{37}+H^+$, 25%), 268 ($M^{35}+ H^+$, 80), 234 (100), 190 (35), 174 (25), 142 (25) and 91 (35); Found: $M^{35}+H^+$, 268.6743. $C_{13}H_{14}ClNO_3$ requires for $M^{35}+H^+$, 268.6740.

Methyl 2-(N-benzyl-2,2-dichloroethanamido)propenoate (**10**)

Following the general procedure dichloroacetyl chloride (1.01 ml, 10.51 mmol) and triethylamine (1.47 ml, 10.51 mmol) were added to (**16**)[15] (1.00 g, 4.78 mmol) in dichloromethane (30 ml) followed by a further 1.1 equivalents of triethylamine (0.73 ml, 5.23 mmol) to cause elimination (1 h). Column chromatography (silica, dichloromethane) afforded the title compound (**10**) (1.28 g, 89%) as a pale yellow oil: R_f 0.37 (dichloromethane); υ_{max} (thin film) 1731 (s), 1693 (s), 1633 (m), 1438 (m), 1315 (m), 1216 (m), 1198 (m), 1169 (m), 1090 (w), 911 (s), 807 (m) and 731 (m) cm^{-1}; δ_H (270 MHz, d_8-toluene at 80°C) 7.06-7.00 (5H, m, aromatics), 5.92 (1H, s, C<u>H</u>=C), 5.89 (1H, s, C<u>H</u>Cl_2), 5.06 (1H, s, C<u>H</u>=C), 4.54 (2H, s, N$C\underline{H}_2$Ph) and 3.30 (3H, s, O$C\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 163.8, 163.3 ($\underline{C}O_2CH_3$ and N<u>C</u>O), 136.3 ($\underline{C}$=CH_2), 135.3 (aromatic <u>C</u>=CH), 130.6 ($\underline{C}H_2$=C), 128.7, 128.1, 127.6 (aromatic <u>C</u>H=C), 64.2 ($\underline{C}HCl_2$), 53.0 (N$\underline{C}H_2$Ph) and 52.1 (O$\underline{C}H_3$); *m/z* (CI, NH_3) 306 (M^{37}+H^+, 35%), 302 (M^{35}+H^+, 60), 268 (25), 232 (30), 190 (85), 175 (70), 108 (20) and 91 (100); Found: M^{35}+H^+, 302.0350. $C_{13}H_{13}Cl_2NO_3$ requires for M^{35}+H^+, 302.0351.

Methyl (N-benzyl-2,2,2-trichloroethanamido)propenoate (**11**)

Trichloroacetyl chloride (1.39 ml, 12.42 mmol) in dry dichloromethane (2 ml) was added to a solution of *N*-benzyl serine (**16**)[15] (1.18 g, 5.65 mmol) in dry dichloromethane (40 ml) containing triethylamine (1.73 ml, 12.42 mmol) following the general procedure. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62 ml, 0.44 mmol) was added to the solution which was then heated at reflux for 4 days. Column chromatography (silica; petroleum ether-diethyl ether 1:1) afforded the title compound (**11**) (124 mg, 88%) as a pale yellow oil. R_f 0.46 (1:1 petroleum ether-diethyl ether); υ_{max} (thin film) 1734 (s), 1688(s), 1635 (m), 1439 (m), 1314 (m), 1217 (m), 1196 (m), 1171 (m), 1092 (w), 914 (s) and 807 (m) cm^{-1}; δ_H (d_8-toluene at 80°C, 270 MHz) 7.17-6.93 (5H, m, aromatics), 6.06 (1H, s, C<u>H</u>=C), 5.17 (1H, s, C<u>H</u>=C), 4.72 (2H, br s, $C\underline{H}_2$Ph) and 3.36 (3H, s, O$C\underline{H}_3$); δ_C ($CDCl_3$, 67.5 MHz) 163.6, 160.3 ($\underline{C}O_2$Me and N<u>C</u>O), 136.5, 135.3 (<u>C</u>=CH and $\underline{C}$=CH_2), 128.9 (br, $\underline{C}H_2$=C), 128.7, 128.3, 127.5 (<u>C</u>H=C), 92.7 ($\underline{C}Cl_3$), 54.7 ($\underline{C}H_2$Ph) and 52.7 (O$\underline{C}H_3$); *m/z* (CI, NH_3) 359 (M^{37}+NH_4^+, 5%), 353 (M^{35}+NH_4^+, 15), 298 (65), 253 (35), 236 (20), 190 (100), 175 (70), 108 (20) and 91 (35); Found: M^{35}+NH_4^+, 353.0231. $C_{13}H_{12}Cl_3NO_3$ requires for M^{35}+NH_4^+, 353.0226.

Methyl 2-(2-chloropropanamido)propenoate (**21**)

Following the general procedure, D,L-serine methyl ester hydrochloride (0.21 g, 0.88 mmol) was reacted with triethylamine (0.40 ml, 2.90 mmol) and 2-chloropropionyl chloride (0.24 g, 1.94 mmol) in ethyl acetate (40 ml). Column chromatography (silica; ethyl acetate) afforded the alkene (**21**) (0.13 g, 76%) as a colourless oil; R_f 0.68 (ethyl acetate); υ_{max} (thin film) 3373 (br), 1727 (vs), 1693 (vs), 1637 (s), 1528 (s), 1442 (m), 1375 (w), 1330 (m), 1204 (m), 1172 (m), 1074 (w), 995 (w), 955 (w), 806 (w) and 730 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.89 (1H, br s, N<u>H</u>), 6.65 (1H, s, C=C<u>H</u>), 5.90 (1H, s, C=C<u>H</u>), 4.44 (1H, q, *J* =7, $CH_3C\underline{H}$), 3.85 (3H, s, O$C\underline{H}_3$) and 1.72 (3H, d, *J* =7, $C\underline{H}_3$CH); δ_C (67.5 MHz, $CDCl_3$) 171.3, 168.1 (N<u>C</u>O and $\underline{C}O_2CH_3$), 130.5 ($\underline{C}$=CH_2), 109.7 (C=$\underline{C}H_2$), 55.8, 53.1 (O$\underline{C}H_3$ and $CH_3\underline{C}$H) and 24.1 ($\underline{C}H_3$CH); *m/z* (CI, NH_3) 211 (M^{37}+NH_4^+, 10%), 209 (M^{35}+NH_4^+, 45), 194 (M^{37}+H^+, 30), 192 (M^{35}+H^+, 100), 156 (25), 132 (15) and 102 (30); Found: M^{35}+H^+, 192.0424. $C_7H_{10}ClNO_3$ requires for M^{35}+H^+, 192.0427.

Methyl 2-(N-benzyl-2-iodoethanamido)propenoate (**7**)

Sodium iodide (1.09 g, 7.30 mmol) was dissolved in acetone (20 ml) and added to the chloroalkene (**5**) (650 mg, 2.43 mmol). After stirring overnight a precipitate formed so the solvent was removed *in vacuo* and the residue was dissolved in diethyl ether and washed with water, brine, dried (magnesium sulfate) and concentrated to afford the crude iodide. Column chromatography (silica; petroleum ether-diethyl ether, 1:1) afforded the alkene (**7**) (829 mg, 95%) as a colourless oil; R_f 0.36 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 1728 (vs), 1660 (vs), 1631 (s), 1435 (m), 1354 (m), 1314 (w), 1087 (s), 981 (m), 802 (m) and 699 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.41-7.20 (5H, m, aromatics), 6.36 (1H, s, C$\underline{H}$=C), 5.59 (1H, s, C$\underline{H}$=C), 4.82-4.59 (2H, br s, NC$\underline{H}_2$Ph), 3.81 (3H, s, OC$\underline{H}_3$) and 3.62 (2H, s, C$\underline{H}_2$I); δ_C (67.5 MHz, $CDCl_3$) 167.6, 163.8 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 137.5 ($\underline{C}$=CH_2), 136.2 ($\underline{C}$=CH), 128.9, 128.5, 127.4 ($\underline{C}$H=C), 126.9 ($\underline{C}H_2$=C), 52.9 (O$\underline{C}H_3$), 51.7 (N$\underline{C}H_2$Ph) and 29.6 ($\underline{C}H_2$I); *m/z* (CI, NH_3) 377 (M+ NH_4^+, 100%), 360 (M+H^+, 60), 251 (15) and 234 (25); Found: M+ NH_4^+, 377.0353. $C_{13}H_{14}INO_3$ requires for M+ NH_4^+, 377.0362.

General Procedure for Radical Cyclisation

A 0.014 mol dm^{-1} solution containing tributyltin hydride (1.1 eq.) and azobisisobutyronitrile (0.1 eq.) in benzene or toluene (29-81ml) was added dropwise over 1 h *via* a syringe pump to a 0.024 mol dm^{-1} solution of the alkene (0.36-0.63 mmol) in boiling benzene or toluene whilst the latter was stirred under nitrogen. The solution was then heated at reflux for a further 3 hours and the solvent removed *in vacuo*. Diethyl ether (10-15ml) and aqueous potassium fluoride (8% aq., 10-15 ml) was added to the residue and the mixture stirred for 2 h. The organic layer was separated, washed with water, brine, dried (magnesium sulfate) and evaporated under reduced pressure to afford crude product which was purified by flash column chromatography (silica).

*Radical cyclisation of methyl 2-(*N*-benzyl-2-chloroethanamido)propenoate* (**5**)

Following the general procedure, alkene (**5**) (0.13 g, 0.48 mmol) was reacted with tributyltin hydride (0.14g, 0.52mmol) and azobisisobutyronitrile (8 mg) in benzene (37 ml). Column chromatography (silica; petroleum ether-ethyl acetate, 1:3) afforded *methyl (2R,S)-*N*-benzylpyroglutamate* (**17**) (0.6 g, 52%) and *methyl 2-(*N*-benzylethanamido)propenoate* (**18**) (0.01 g, 8%).

*Methyl (2R,S)-*N*-benzylpyroglutamate* (**17**): R_f 0.38 (petroleum ether-ethyl acetate, 1:3); υ_{max} (thin film) 1744 (vs), 1691 (vs), 1417 (m), 1358 (m), 1205 (w), 1174 (m), 1080 (m), 1039 (m), 990 (m), 729 (w) and 648 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.38-7.21 (5H, m, aromatics), 5.00 (1H, d, J =15, NC$\underline{H}$Ph), 4.05 (1H, m, NC$\underline{H}$), 4.00 (1H, d, J =15 Hz, NC$\underline{H}$Ph), 3.69 (3H, s, OC$\underline{H}_3$) and 2.66-2.03 (4H, m, COC$\underline{H}_2$ and CHC$\underline{H}_2$); δ_C (67.5 MHz, $CDCl_3$) 174.9, 172.1 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 135.7 ($\underline{C}$=C), 128.6, 128.4, 127.7 ($\underline{C}$H=C), 58.6 (N$\underline{C}$H), 52.3 (O$\underline{C}H_3$), 45.5 (N$\underline{C}H_2$Ph), 29.4 (CO$\underline{C}H_2$) and 22.6 (CH$\underline{C}H_2$); *m/z* (CI, NH_3) 251 (M+NH_4^+, 10%), 234 (M+H^+,100), 174 (10), 35 (25); Found: M+H^+, 234.1134. $C_{13}H_{15}NO_3$ requires for M+H^+, 234.1136.

*Methyl 2-(*N*-benzylethanamido)propenoate* (**18**): R_f 0.51 (petrolum ether-ethyl acetate, 1:3); υ_{max} (thin film) 1729 (vs), 1668 (vs), 1632 (s), 1438 (m), 1402 (m), 1315 (w), 1254 (m), 1203 (m), 1172 (w), 1085 (m), 978 (m), 864 (w), 732 (m) and 702 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.22-7.15 (5H, m, aromatics), 6.43 (1H, s, C$\underline{H}$=C), 5.45 (1H, s, C$\underline{H}$=C), 4.61 (2H, s, NC$\underline{H}_2$Ph), 3.82 (3H, s, OC$\underline{H}_3$) and 2.11 (3H, s, COC$\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 170.1, 165.6 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 138.9 ($\underline{C}$=CH_2), 136.9 ($\underline{C}$=C), 128.1 (C=$\underline{C}H_2$), 128.7, 128.2, 127.5 ($\underline{C}$H=C), 52.7 (O$\underline{C}H_3$), 50.7 (N$\underline{C}H_2$Ph) and 22.0 (NCO$\underline{C}H_3$); *m/z* (CI, NH_3) 234 (M+H^+, 100%), 190 (15), 91 (20); Found: M+H^+, 234.1135. $C_{13}H_{15}NO_3$ requires for M+H^+, 234.1130.

Radical cyclisation of methyl 2-(N-benzyl-2-bromoethanamido)propenoate (**6**)

Following the general procedure, alkene (**6**) (74 mg, 0.24 mmol) was reacted with tributyltin hydride (0.76 mg, 0.26mmol) and azobisisobutyronitrile (4 mg) in benzene (19 ml). Column chromatography (silica; petroleum ether-ethyl acetate, 1:3) afforded *methyl (2R,S)-N-benzylpyroglutamate* (**17**) (24 mg, 47%) and *methyl 2-(N-benzylethanamido)propenoate* (**18**) (4 mg, 8%).

Radical cyclisation of methyl 2-(N-benzyl-2-iodoethanamido)propenoate (**7**)

Following the general procedure, alkene (**7**) (145 mg, 0.40 mmol) was reacted with tributyltin hydride (0.12 ml, 0.44 mmol) and azobisisobutyronitrile (7 mg) in benzene (31 ml). Column chromatography (silica; petroleum ether-ethyl acetate, 1:3) afforded *methyl (2R,S)-N-benzylpyroglutamate* (**17**) (32 mg, 38%) and *methyl 2-(N-benzylethanamido)propenoate* (**18**) (7 mg, 7%).

Radical cyclisation of methyl 2-(2-chloropropanamido)propenoate (**21**)

Following the general procedure, the alkene (**21**) (0.11 g, 0.57 mmol) was treated with tributyltin hydride (0.17 ml, 0.63 mmol) and azobisisobutyronitrile (9 mg) in benzene (44 ml). After 3 h, t.l.c. indicated no starting material remained. Work-up afforded crude product which on analysis by ^{1}H n.m.r., infrared spectroscopy and mass spectrometry showed no pyroglutamate (**22**) had been formed.

Radical cyclisation of methyl 2-(N-benzyl-2-chloropropanamido)propenoate (**8**)

Following the general procedure, the alkene (**8**) (0.14 g, 0.50 mmol) was treated with tributyltin hydride (0.15 ml, 0.55 mmol) and azobisisobutyronitrile (9 mg) in benzene (39 ml). The crude material was purified by column chromatography (silica; diethyl ether) to afford *methyl (2R,S,4R,S)-N-benzyl-4-methylpyroglutamate* (**23**) (60 mg, 47%) as a colourless oil as a mixture of inseparable diastereoisomers in the ratio 1:1.75; R_f 0.39 (diethyl ether); *Major diastereoisomer*; υ_{max} (thin film) 1745 (vs), 1672 (vs), 1455 (m), 1422 (m), 1357 (m), 1171 (w), 1081 (m), 1078 (w) and 702 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.23-7.08 (5H, m, aromatics), 5.00 (1H, d, J =15, NC$\underline{H}$Ph), 3.93 (1H, d, J =15, NC$\underline{H}$Ph), 3.89 (1H, m, NC$\underline{H}$), 3.62 (3H, s, OC$\underline{H}_3$), 2.57-1.70 (3H, m, $CH_3C\underline{H}$ and NCHC$\underline{H}_2$) and 1.25 (3H, d, J=7, CHC$\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 177.4, 172.3 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 135.8 ($\underline{C}$=C), 128.6, 128.3, 127.7 ($\underline{C}$H=C), 56.9, 52.3 (N$\underline{C}$H and O$\underline{C}H_3$), 45.7 (N$\underline{C}H_2$Ph), 35.9, 31.9 ($CH_3\underline{C}H$ and $\underline{C}H_2CH$) and 16.7 (CH$\underline{C}H_3$); *m/z* (CI, NH_3) 265 (M+NH_4^+, 45%), 248 (M+H^+, 100), 188 (30), 160 (25) and 91 (55); Found: M+H^+, 248.1208. $C_{14}H_{16}NO_3$ requires for M+H^+, 248.1204. *Minor diastereoisomer*; The presence of the minor diastereoisomer was indicated by: δ_H (270 MHz, $CDCl_3$) 4.91 (1H, d, J=15, NC$\underline{H}$Ph), 3.84 (1H, d, J=15, NC$\underline{H}$Ph), 3.58 (3H, s, OC$\underline{H}_3$), 2.69-2.58 (1H, m, NCHC$\underline{H}$) and 2.36-2.28 (1H, m, NCHC$\underline{H}$); δ_C (67.5 MHz, $CDCl_3$) 177.1, 172.0 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 135.7 ($\underline{C}$=C), 128.5, 128.0, 127.6 ($\underline{C}$H=C), 45.5 (N$\underline{C}H_2$Ph), 34.9, 32.0 ($CH_3\underline{C}H$ and $\underline{C}H_2CH$) and 16.0 (CH$\underline{C}H_3$).

Radical cyclisation of methyl 2-(N-benzyl-2-chloro-2-phenylethanamido)propenoate (**9**) *in benzene*

Following the general procedure, the alkene (**9**) (0.13 g, 0.38 mmol) was treated with tributyltin hydride (122 mg, 0.42 mmol) and azobisisobutyronitrile (6 mg) in benzene (30 ml). The crude material was purified by column chromatography (silica; petroleum ether-diethyl ether, 2:3) to afford *methyl (2R,S,4R,S)-*

(N-benzyl-4-phenyl)pyroglutamate (**24**) (70 mg, 56%) as a colourless oil as a mixture of inseparable diastereoisomers in the ratio 1:2.1; R_f 0.22 (petroleum ether-diethyl ether, 2:3); *Major diastereoisomer*; υ_{max} (thin film) 1741 (vs), 1702 (vs), 1495 (m), 1415 (m), 1356 (w), 1204 (m), 1172 (m), 1061 (w), 1028 (w), 735 (m) and 700 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31-7.14 (10H, m, aromatics), 5.13 (1H, d, J =15, NC<u>H</u>Ph), 4.07-3.60 (6H, m, NC<u>H</u>Ph, NC<u>H</u>, OC<u>H</u>$_3$ and PhC<u>H</u>CO), 2.79-2.70 (1H, m, NCHC<u>H</u>) and 2.13-2.03 (1H, m, NCHC<u>H</u>); δ_C (67.5 MHz, $CDCl_3$) 179.2, 175.8 (N<u>C</u>O and <u>C</u>O$_2$CH$_3$), 137.9, 135.6 (2 x <u>C</u>=CH), 128.7, 128.6, 128.5, 128.0, 127.8, 127.2 (<u>C</u>H=C), 56.7 (N<u>C</u>H), 52.5 (O<u>C</u>H$_3$), 47.2 (Ph<u>C</u>HCO), 45.8 (N<u>C</u>H$_2$Ph) and 31.7 (CH<u>C</u>H$_2$); *m/z* (CI, NH_3) 310 ($M+H^+$, 100%), 269 (25), 250 (35) and 91 (35); Found: $M+H^+$, 310.1438. $C_{19}H_{19}NO_3$ requires for $M+H^+$, 310.1443. *Minor diastereoisomer*; The presence of the minor diastereoisomer was indicated by: δ_H (270 MHz, $CDCl_3$) 5.00 (1H, d, J =15, NC<u>H</u>Ph), 2.54-2.45 (1H, m, NCHC<u>H</u>), 2.31-2.22 (1H, m, NCHC<u>H</u>); δ_C (67.5 MHz, $CDCl_3$) 179.8, 176.1 (N<u>C</u>O and <u>C</u>O$_2$CH$_3$), 138.8, 137.2 (2 x <u>C</u>=CH), 57.0 (N<u>C</u>H), 52.4 (O<u>C</u>H$_3$), 47.5 (Ph<u>C</u>HCO), 46.1 (N<u>C</u>H$_2$Ph) and 32.8 (CH<u>C</u>H$_2$).

Radical cyclisation of methyl 2-(N-benzyl-2-chloro-2-phenylethanamido)propenoate (**9**) *in toluene*

Following the general procedure, the alkene (**9**) (0.13 g, 0.38 mmol) was treated with tributyltin hydride (112 mg, 0.42 mmol) and azobisisobutyronitrile (6 mg) in toluene (30 ml). The crude material was purified by column chromatography (silica; petroleum ether-diethyl ether, 2:3) to afford *methyl (2R,S,4R,S)-N-benzyl-4-phenylpyroglutamate* (**24**) (61 mg, 52%) as a colourless oil as a mixture of inseparable diastereoisomers in the ratio 1:2.1.

Radical cyclisation of methyl 2-(N-benzyl-2,2-dichloroethanamido)propenoate (**10**) *using 1.1 equivalents of tributyltin hydride*

Following the general procedure, alkene (**10**) (148 mg, 0.49 mmol) was reacted with tributyltin hydride (0.16 ml, 0.54 mmol) and azobisisobutyronitrile (8 mg) in benzene (39 ml). Column chromatography (silica; ethyl acetate-dichloromethane, 1:10) afforded *methyl (2R,S,4R,S)-(N-benzyl-4-chloro)pyroglutamate* (**25**) (44 mg, 33%) as a mixture of diastereoisomers in the ratio 1:3, and the reduced pyroglutamate, *methyl (2R,S)-N-benzylpyroglutamate* (**17**) (41 mg, 36%).

Methyl (2R,S,4R,S)-(N-benzyl-4-chloro)pyroglutamate (**25**); R_f 0.37 (ethyl acetate-dichloromethane, 1:10); *Major diastereoisomer*; υ_{max} (thin film) 1746 (s), 1715 (s), 1455 (m), 1215 (m), 1172 (m), 1080 (w), 1017 (w) and 710 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31-7.11 (5H, m, aromatics), 4.94 (1H, d, J=15, NC<u>H</u>Ph), 4.64 (1H, d, J=15, NC<u>H</u>Ph), 4.53 (1H, appt t, J=8, C<u>H</u>Cl), 3.97 (1H, dd, J=8 and 3, NC<u>H</u>), 3.60 (3H, s, OC<u>H</u>$_3$), 2.63-2.54 (1H, m, NCHC<u>H</u>) and 2.41-2.29 (1H, m, NCHC<u>H</u>); δ_C (67.5 MHz, $CDCl_3$) 170.9, 170.3 (<u>C</u>O$_2$CH$_3$ and N<u>C</u>O), 134.6 (<u>C</u>=CH), 128.9, 128.5, 128.1 (<u>C</u>H=C), 56.5 (N<u>C</u>H), 53.1 (<u>C</u>HCl), 52.6 (O<u>C</u>H$_3$), 46.3 (N<u>C</u>H$_2$Ph) and 34.1 (NCH<u>C</u>H$_2$); *m/z* (CI, NH_3) 268 ($M^{37}+H^+$, 30), 266 ($M^{35}+H^+$, 100), 232 (25), 208 (10) and 91 (15); Found: $M^{37}+H^+$, 268.0742. $C_{13}H_{14}ClNO_3$ requires for $M^{37}+H^+$, 268.0741.

Minor diastereoisomer. The presence of the minor diastereoisomer was detected by; δ_H (270 MHz, $CDCl_3$) 5.11 (1H, d, J=15, NC<u>H</u>Ph), 4.31 (1H, dd, J=8 and 3, C<u>H</u>Cl), 4.08 (1H, d, J=15, NC<u>H</u>Ph), 3.89 (1H, dd, J=12 and 6, NC<u>H</u>) and 3.70 (3H, s, OC<u>H</u>$_3$); δ_C (67.5 MHz, $CDCl_3$) 56.2 (N<u>C</u>H), 52.7 (O<u>C</u>H$_3$) and 33.7 (NCH<u>C</u>H$_2$).

*Radical cyclisation of methyl 2-(*N*-benzyl-2,2-dichloroethanamido)propenoate* (**10**) *using 2.2 equivalents of tributyltin hydride*

Following the general procedure, alkene (**10**) (152 mg, 0.52 mmol) was reacted with tributyltin hydride (162 mg, 0.56 mmol) and azobisisobutyronitrile (9 mg) in benzene (40 ml). After 3 h, a further equivalent of tributyltin hydride (162 mg, 0.56 mmol) and azobisisobutyronitrile (9 mg) in benzene (2 ml) was added and the solution was heated at reflux for an additional 2 h. Column chromatography (silica; ethyl acetate-dichloromethane, 1:10) afforded the reduced pyroglutamate, *methyl (2R,S)-*N*-benzylpyroglutamate* (**17**) (74 mg, 70%) as a colourless oil.

*Radical cyclisation of methyl (2R,S)-2-(*N*-benzyl-2,2,2-trichloroethanamido)propenoate* (**11**) *using 1.1 equivalents of tributyltin hydride*

Following the general procedure, alkene (**11**) (112 mg, 0.33 mmol) was reacted with tributyltin hydride (107 mg, 0.37 mmol) and azobisisobutyronitrile (5 mg) in benzene (26 ml). Column chromatography (silica; diethyl ether) afforded a mixture of *methyl (2R,S)-(*N*-benzyl-4,4-dichloro)pyroglutamate* (**26**) (81 mg, 81%), together with the monochlorinated pyroglutamate, *methyl (2R,S,4R,S)-(*N*-benzyl-4-chloro)pyroglutamate* (**25**) (4 mg, 4 %).

*Methyl (2R,S)-(*N*-benzyl-4,4-dichloro)pyroglutamate* (**26**); R_f 0.69 (diethyl ether); υ_{max} (thin film) 1745 (s), 1711 (s), 1456 (m), 1217 (m), 1170 (m), 1079 (w), 1015 (w) and 715 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.29-7.09 (5H, m, aromatics), 5.11 (1H, d, J=16, NC<u>H</u>Ph), 4.12 (1H, d, J=16, NC<u>H</u>Ph), 3.88 (1H, dd, J=7 and 5, NC<u>H</u>), 3.68 (3H, s, OC<u>H</u>$_3$) and 3.06-2.94 (2H, m, NCHC<u>H</u>$_2$); δ_C (67.5 MHz, $CDCl_3$) 169.4, 166.7 (<u>C</u>O$_2$CH$_3$ and N<u>C</u>O), 134.1 (<u>C</u>=CH), 129.0, 128.5, 128.3 (<u>C</u>H=C), 79.7 (<u>C</u>Cl$_2$), 54.5 (N<u>C</u>H), 52.9 (O<u>C</u>H$_3$), 46.7 and 45.4 (N<u>C</u>H$_2$Ph and NCH<u>C</u>H$_2$); m/z (CI, NH_3) 306 (M^{37}+H^+, 5%), 302 (M^{35}+H^+, 25), 285 (40), 268 (30), 154 (20) and 108 (15); Found: M+NH_4^+, 319.0624. $C_{13}H_{13}Cl_2NO_3$ requires for M+NH_4^+, 319.0616.

*Radical cyclisation of methyl 2-(*N*-benzyl-2,2,2-trichloroethanamido) propenoate* (**11**) *using 3.3 equivalents of tributyltin hydride*

Following the general procedure, alkene (**11**) (101 mg, 0.30 mmol) was reacted with tributyltin hydride (97 mg, 0.33 mmol) and azobisisobutyronitrile (5 mg) in benzene (24 ml). After 3 h, a further 2.2 equivalents of tributyltin hydride (193 mg, 0.66 mmol) and azobisisobutyronitrile (10 mg) in benzene (2 ml) was added and the solution was heated at reflux for an additional 2 h. Column chromatography (silica; diethyl ether) afforded the reduced pyroglutamate, *methyl (2R,S)-*N*-benzylpyroglutamate* (**17**) (59 mg, 84%) as a colourless oil.

*Methyl 2-(*N*-benzyl-2-phenylsulfanylethanamido)propenoate* (**27**)

To a stirred solution of the *N*-benzyl serine derivative (**16**)[15] (1.39 g, 6.63 mmol) in dry dichloromethane (50 ml) was added triethylamine (1.02 ml, 7.29 mmol), thiophenoxyacetic acid (1.23 g, 7.29 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (1.86 g, 7.29 mmol). After 3 h, the solution was washed with water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford crude amide which upon column chromatography (silica, diethyl ether) afforded amide (1.40 g, 59%) as a colourless oil.

To a stirred solution of this amide (820 mg, 2.28 mmol) in dry dichloromethane (40 ml) at 0°C was added triethylamine (0.35 ml, 2.51 mmol) followed by the dropwise addition of dichloroacetyl chloride (0.24 ml, 2.51 mmol) in dichloromethane (2 ml). After 0.5 h, the solution was allowed to warm to room temperature and after an additional 2 h, the solution was washed with water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford crude alkene. Column chromatography (silica; petroleum ether-diethyl ether, 1:1) afforded the alkene (**27**) (710 mg, 85%) as a pale yellow oil; R_f 0.50 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 1730 (s), 1660 (s) and 1631 (s), 1528 (s), 1442 (m), 1375 (w), 1330 (m), 1204 (m), 1172 (m), 1074 (w), 995 (w), 955 (w), 806 (w) and 730 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.34-7.10 (10H, m, aromatics), 6.22 (1H, s, C<u>H</u>=C), 5.17 (1H, s, C<u>H</u>=C), 4.60 (2H, br s, $NC\underline{H}_2Ph$), 3.68 (3H, s, $OC\underline{H}_3$) and 3.56 (2H, s, $C\underline{H}_2SPh$); δ_C (67.5 MHz, $CDCl_3$) 169.1, 163.8 (N<u>C</u>O and $\underline{C}O_2CH_3$), 137.3 ($\underline{C}=CH_2$), 136.1, 134.4 (2x CH=<u>C</u>), 130.8, 129.3, 128.9, 128.3, 127.3, 127.0 (aromatic C=<u>C</u>H and $\underline{C}H_2=C$), 52.8 ($O\underline{C}H_3$), 51.2 ($N\underline{C}H_2Ph$) and 37.1 ($\underline{C}H_2SPh$); *m/z* (CI, NH_3) 342 ($M+H^+$, 100%), 234 (30) and 192 (20); Found: $M+H^+$, 342.1156. $C_{19}H_{19}NO_3S$ requires for $M+H^+$, 342.1164.

Methyl 2-(N-benzyl-2-chloro-2-phenylsulfanylethanamido)propenoate (**28**)

To a stirred solution of the alkene (**27**) (281 mg, 0.83 mmol) in carbon tetrachloride (20 ml) at 0°C was added *N*-chlorosuccinimide (121 mg, 0.91 mmol). After 1 h, the solvent was removed *in vacuo* and the residue immediately chromatographed (silica, petroleum ether-diethyl ether, 1:1) to afford the chloro-compound (**28**) (218g, 70%) as a pale yellow oil; R_f 0.42 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 1728 (vs), 1660 (vs), 1631 (s), 1435 (m), 1354 (m), 1314 (w), 1087 (s), 981 (m), 802 (m) and 699 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.47-7.19 (10H, m, aromatics), 6.32 (1H, s, C<u>H</u>=C), 5.55 (1H, s, C<u>H</u>=C), 5.45 (1H, s, C<u>H</u>(Cl)SPh), 4.65 (2H, br s, $NC\underline{H}_2Ph$) and 3.68 (3H, s, $OC\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 165.2, 163.6 (N<u>C</u>O and $\underline{C}O_2CH_3$), 137.5 ($\underline{C}=CH_2$), 137.9, 136.8 (2x CH=<u>C</u>), 129.1 ($\underline{C}H_2=C$), 131.1, 129.3, 128.7, 128.7, 128.0, 127.9 (aromatic C=<u>C</u>H), 66.1 (<u>C</u>H(Cl)SPh), 52.9 ($O\underline{C}H_3$) and 52.7 ($N\underline{C}H_2Ph$); *m/z* (CI, NH_3) 378 ($M^{37}+H^+$, 10%), 376 ($M^{35}+H^+$, 35%), 340 (100), 299 (20), 232 (75), 108 (20) and 91(60); Found: $M^{35}+H^+$, 376.0772. $C_{19}H_{18}ClNO_3S$ requires for $M^{35}+H^+$, 376.0774.

*Radical cyclisation of methyl 2-(*N*-benzyl-2-chloro-2-phenylsulfanylethanamido)propenoate* (**28**)

Following the general procedure, alkene (**28**) (149 mg, 0.40 mmol) was reacted with tributyltin hydride (127 mg, 0.44 mmol) and azobisisobutyronitrile (7 mg) in benzene (31 ml). Column chromatography (silica; petroleum ether-diethyl ether, 1:1) afforded *methyl (2R,S,4R,S)-(*N*-benzyl-4-phenylsulfanyl)pyroglutamate* (**29**) (63 mg, 46%) as a colourless oil as a mixture of diastereomers in the ratio of 1.5:1; R_f 0.23 (petroleum ether-diethyl ether, 1:1); *major diastereomer*; υ_{max} (thin film) 2952 (s), 1743 (s), 1697 (s), 1438 (m), 1213 (m), 1170 (w), 1024 (m), 744 (w) and 700 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.50-6.96 (10H, m, aromatics), 5.05 (1H, d, *J*=15, NC<u>H</u>Ph), 3.91 (1H, d, *J*=15, NC<u>H</u>Ph), 3.88-3.71 (2H, m, C<u>H</u>SPh and NC<u>H</u>), 3.59 (3H, s, $OC\underline{H}_3$) and 2.69-2.08 (2H, m, $NCHC\underline{H}_2$); δ_C (67.5 MHz, $CDCl_3$) 172.2, 171.4 ($\underline{C}O_2CH_3$ and N<u>C</u>O), 135.7 (<u>C</u>=CH), 133.3, 131.9, 128.7, 128.5, 128.3, 127.9 (<u>C</u>H=C), 56.5 (N<u>C</u>H), 52.5 ($O\underline{C}H_3$), 46.7 (<u>C</u>HSPh), 46.2 ($N\underline{C}H_2Ph$) and 30.4 ($NCH\underline{C}H_2$); *m/z* (CI, NH_3) 342 ($M+H^+$, 100%), 232 (15) and 91 (15); Found: $M+H^+$, 342.1167. $C_{19}H_{19}NO_3S$ requires for $M+H^+$, 342.1164. The *minor diastereomer* was evident from: δ_H (270 MHz, $CDCl_3$) 4.96 (1H, d, *J*=15, NC<u>H</u>Ph), 4.04 (1H, d,

J=15, NC$\underline{H}$Ph) and 3.61 (O$\underline{C}H_3$); δ_C (67.5 MHz, $CDCl_3$) 171.5 (N$\underline{C}$O), 56.6 (N$\underline{C}$H), 46.9 ($\underline{C}$HSPh) and 30.7 (NCH$\underline{C}H_2$).

*Methyl 2-(2-chloro-*N*-(3-methyl-2-butenyl)ethanamido)propenoate* (**30a**)

To a stirred solution of *methyl-(2R,S)-(3-*tert*-butyldimethylsiloxy)-2-(3-methyl-2-butenyl)amino propionate*[16] (966 mg, 3.21 mmol) in dry dichloromethane (40 ml) at 0°C was added triethylamine (0.49 ml, 3.63 mmol) followed by chloroacetyl chloride (0.34 ml, 3.63 mmol) which was added dropwise as a solution in dichloromethane (2 ml) followed by stirring for 0.5 h. The solution was gradually warmed to room temperature and washed with water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford the crude amide (872 mg, 72%) which was purified by column chromatography (silica; hexane-ethyl acetate, 4:1).

p-Toluenesulfonic acid (catalytic) was added to a stirred solution of the silyl amide (850 mg, 2.25 mmol) in methanol (40 ml) and the mixture was stirred overnight. The methanol was removed *in vacuo*, the residue dissolved in ethyl acetate and washed with water, brine, dried (magnesium sulfate) and evaporated to afford crude alcohol which was purified by column chromatography (553 mg, 90%) (silica, diethyl ether).

To a solution of the alcohol (530 mg, 2.02 mmol) in dry dichloromethane (30 ml) at 0°C was added triethylamine (0.31 ml, 2.22 mmol) followed by the dropwise addition of dichloroacetyl chloride (0.21 ml, 2.22 mmol) in dichloromethane (3 ml). The solution was allowed to warm to room temperature after 0.5 h and after an additional 1 h, t.l.c. indicated no starting material remained so a further equivalent of triethylamine was added and the solution turned black as elimination occurred (6 h). The solution was then washed with 10% aq. citric acid, water, brine, dried (magnesium sulfate) and evaporated *in vacuo*. Column chromatography (silica, petroleum ether-diethyl ether, 1:1) afforded the desired alkene (**30a**) (297 mg, 60%) as a pale yellow oil. R_f 0.48 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 2954 (s), 1736 (s), 1665 (s), 1633 (s), 1438 (m), 1380 (w), 1213 (m), 1170 (s), 1089 (w), 1002 (w) and 813 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.41 (1H, s, C$\underline{H}$=C), 5.76 (1H, s, C=C$\underline{H}$), 5.10 (1H, t, J=7, C=C$\underline{H}CH_2$), 4.40 (2H, br m, C$\underline{H}_2$CH), 4.02 (2H, s, C$\underline{H}_2$Cl), 3.78 (3H, s, OC$\underline{H}_3$), 1.86 (3H, s, C-C$\underline{H}_3$) and 1.74 (3H, s, C-C$\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 165.4, 164.7 ($\underline{C}O_2$Me and N$\underline{C}$O), 139.4 ($\underline{C}=CH_2$), 136.9 ($\underline{C}$=CH), 126.6 ($\underline{C}H_2$=C), 119.6 ($\underline{C}$H=C), 52.1 (O$\underline{C}H_3$), 46.2 ($\underline{C}H_2$-CH=C), 41.6 ($\underline{C}H_2$Cl), 25.5 (CH=C-$\underline{C}H_3$) and 17.8 (CH=C-$\underline{C}H_3$); *m/z* (CI, NH_3) 246 ($M^{35}+H^+$, 100%), 212 (35), 178 (30), 168 (20) and 142 (10); Found: $M^{35}+H^+$, 246.0902. $C_{11}H_{16}ClNO_3$ requires for $M^{35}+H^+$, 246.0897.

Methyl 2-(2,2-dichloro-N-(3-methyl-2-butenyl)ethanamido)propenoate (**30b**)

To a stirred solution of *methyl-(2R,S)-(3-*tert*-butyldimethylsiloxy)-2-(3-methyl-2-butenyl)amino propionate*[16] (1.57 g, 5.22 mmol) in dry dichloromethane (50 ml) at 0°C was added triethylamine (0.80 ml, 5.74 mmol) then dichloroacetyl chloride (0.55 ml, 5.74 mmol) was added dropwise as a solution in dichloromethane (2 ml) followed by stirring for 0.5 h. The solution was gradually warmed to room temperature and washed with water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford the crude amide (2.09 g, 98%) which was purified by column chromatography (silica, petroleum ether-ethyl acetate, 4:1).

p-Toluenesulfonic acid (catalytic) was added to a stirred solution of the silyl amide (2.09 g, 5.09 mmol) in methanol (40 ml) and stirring was continued overnight. The methanol was removed *in vacuo* then the residue dissolved in ethyl acetate and washed with water, brine, dried (magnesium sulfate) and evaporated to afford crude alcohol. To a solution of the crude alcohol in dry dichloromethane (40 ml) at 0°C was added triethylamine (0.78 ml, 5.59 mmol) followed by the dropwise addition of dichloroacetyl chloride (0.54 ml, 5.59 mmol) in dichloromethane (2 ml). The solution was allowed to warm to room temperature after 0.5 h and after an additional 1 h, t.l.c. indicated no starting material remained so a further equivalent of triethylamine was added and the solution turned black as elimination occurred (6 h). The solution was then washed with 10% aq. citric acid, water, brine, dried (magnesium sulfate) and evaporated *in vacuo* which was followed by purification using column chromatography (silica, petroleum ether-diethyl ether, 1:1) to afford the desired alkene (**30b**) (1.21 g, 85%) as a colourless oil; R_f 0.59 (petroleum ether-diethyl ether, 1:1); υ_{max} (thin film) 1731 (s), 1690 (s), 1632 (s), 1438 (m), 1209 (m), 1109 (m), 809 (s) and 732 (m) cm^{-1}; δ_H (270 MHz, d_8-toluene at 80°C) 6.51 (1H, s, C$\underline{H}$=C), 6.37 (1H, s, C$\underline{H}Cl_2$), 5.79 (1H, s, C$\underline{H}$=C), 5.45 (1H, t, *J*=7, C$\underline{H}$=C), 4.46 (2H, d, *J*=7, NC$\underline{H_2}$), 3.80 (3H, s, OC$\underline{H_3}$), 1.89 (3H, s, C$\underline{H_3}$) and 1.80 (3H, s, C$\underline{H_3}$); δ_C (67.5 MHz, $CDCl_3$) 163.3, 163.0 ($\underline{C}O_2CH_3$ and N$\underline{C}$O), 138.6 ($\underline{C}$=CH), 136.7 ($\underline{C}$=CH), 129.6 ($\underline{C}H_2$=C) 117.0 ($\underline{C}$H=C), 64.2 ($\underline{C}HCl_2$), 52.8 (O$\underline{C}H_3$), 45.9 (N$\underline{C}H_2$), 29.5 ($\underline{C}H_3$CH) and 25.6 ($\underline{C}H_3$CH); *m/z* (CI, NH_3) 297 ($M^{35}+NH_4^+$, 20%), 280 ($M^{35}+H^+$, 100), 244 (25), 210 (20) and 168 (25). Found: $M^{35}+NH_4^+$, 297.0773. $C_{11}H_{15}Cl_2NO_3$ requires for $M^{35}+NH_4^+$, 297.0773.

Methyl 2-(2,2,2-trichloro-N-(3-methyl-2-butenyl)ethanamido)propenoate (**30c**)

To a stirred solution of *methyl-(2R,S)-(3-*tert*-butyldimethylsiloxy)-2-(3-methyl-2-butenyl)amino propionate*[16] (1.90 g, 6.3 mmol) in dry tetrahydrofuran (10 ml) under a nitrogen atmosphere was added *tert*-butylammonium fluoride (6.9 ml of a 1M solution in tetrahydrofuran, 6.9 mmol). The solution was warmed to room temperature and after 0.5 h the solvent was removed *in vacuo* the residue dissolved in ethyl acetate and washed with water, brine, dried (magnesium sulfate) and concentrated to afford crude alcohol. Without purification the alcohol was dissolved in dry dichloromethane (40 ml) at 0°C and treated with triethylamine (1.93 ml, 13.86 mmol) followed by the dropwise addition of trichloroacetyl chloride (1.55 ml, 13.86 mmol) in dichloromethane (4 ml) and the reaction was stirred for 0.5 h. After stirring at room temperature for 2 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (1.03 ml, 6.93 mmol) was added and the solution was heated at reflux for 72 h. The solution was then washed with 10% aq. citric acid, water, brine, dried (magnesium sulfate) and evaporated *in vacuo* to afford crude product. Column chromatography (silica; ethyl acetate-petroleum ether, 1:2) afforded the desired alkene (**30c**) (649 mg, 62%) as a colourless oil; R_f 0.76 (ethyl acetate-petroleum ether, 1:2); υ_{max} (thin film) 1736 (s), 1684 (s), 1631 (s), 1438 (m), 1209 (m), 1109 (m), 809 (s) and 732 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.50 (1H, s, C$\underline{H}$=C), 5.83 (1H, s, C$\underline{H}$=C), 5.21 (1H, t, *J*=7, C=C$\underline{H}CH_2$), 4.25-4.17 (2H, br m, NC$\underline{H_2}$), 3.79 (3H, s, OC$\underline{H_3}$), 1.71 (3H, s, CC$\underline{H_3}$) and 1.60 (3H, s, CC$\underline{H_3}$); δ_C (67.5 MHz, $CDCl_3$) 163.7, 159.9 ($\underline{C}O_2CH_3$ and N$\underline{C}$O), 138.5 ($\underline{C}$=CH), 137.2 (C=$\underline{C}$H), 129.6 ($\underline{C}H_2$=C) 117.2 ($\underline{C}$H=C), 92.6 ($\underline{C}Cl_3$), 52.7 (O$\underline{C}H_3$), 49.5 (N$\underline{C}H_2$), 25.7 ($\underline{C}H_3$CH) and 17.9 ($\underline{C}H_3$CH); *m/z* (CI, NH_3) 331 ($M^{35}+NH_4^+$, 10%), 314 ($M^{35}+H^+$, 95), 280 (30), 246 (25), 168 (100), 108 (25) and 69 (70). Found: $M^{35}+H^+$, 314.0111. $C_{11}H_{14}Cl_3NO_3$ requires for $M^{35}+H^+$, 314.0118.

*Radical cyclisation of methyl 2-(2-chloro-*N*-(3-methyl-2-butenyl)ethanamido)propenoate* (**30a**)

Following the general procedure, alkene (**30a**) (154 mg, 0.63 mmol) was reacted with tributyltin hydride (201 mg, 0.69 mmol) and azobisisobutyronitrile (10 mg) in benzene (49 ml). Column chromatography (silica; diethyl ether) afforded *methyl (2R,S)-(*N*-3-methyl-2-butenyl)pyroglutamate* (**31**) (38 mg, 29%) and *methyl 2-(4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate* (**32**) (12 mg, 12%) as colourless oils.

*Methyl (2R,S)-(*N*-3-methyl-2-butenyl)pyroglutamate* (**31**): R_f 0.34 (diethyl ether); υ_{max} (thin film) 2954 (s), 2926 (s), 1744 (s), 1693 (s), 1439 (m), 1416 (m), 1208 (s), 1173 (s), 1031 (w) and 991 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.00 (1H, t, *J*=8, C=CH), 4.15 (1H, dd, *J*=15 and 8, NCHCH), 4.08 (1H, dd, *J*=9 and 3, NCH), 3.68 (3H, s, OCH_3), 3.56 (1H, dd, *J*=15 and 8, NCHCH), 2.49-2.41 (1H, m, $NCOCH_2$), 2.33-2.19 (2H, m, NCOCH and NCHCH), 2.02-1.94 (1H, m, $NCHCH_2$), 1.65 (3H, s, CCH_3) and 1.57 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 174.8, 172.7 (NCO and CO_2CH_3), 138.1 (C=CH), 117.9 (CH=C), 58.6 (NCH), 52.3 (OCH_3), 39.2 (NCH_2), 29.6 (NCOCH), 25.7 (CCH_3), 22.8 ($NCHCH_2$) and 17.6 (CCH_3); *m/z* (CI, NH_3) 212 ($M+H^+$, 100%), 84 (10) and 35 (15); Found: $M+H^+$, 212.1281. $C_{11}H_{17}NO_3$ requires for $M+H^+$, 212.1287.

Methyl 2-(4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate (**32**). R_f 0.68 (diethyl ether); υ_{max} (thin film) 2956 (s), 1738 (s), 1711 (s), 1629 (m), 1439 (w), 1369 (m) and 1213 (m), 1109 (m), 809 (s) and 732 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.02 (1H, s, CH=C), 5.81 (1H, s, CH=C), 3.87 (3H, s, OCH_3), 3.70 (1H, dd, *J*=9 and 8, NCH), 3.45 (1H, dd, *J*=9 and 8, NCH), 2.66-2.60 (1H, m, NCOCH), 2.34-2.22 (2H, m, NCOCH and NCH_2CH), 1.72-1.68 (1H, m, $CH(CH_3)_2$), 1.01 (3H, d, *J*=7, $CHCH_3$) and 0.99 (3H, d, *J*=7, $CHCH_3$); δ_C (67.5 MHz, $CDCl_3$) 173.8, 163.7 (NCO and CO_2CH_3), 136.4 ($C=CH_2$), 116.6 ($CH_2=C$), 52.4 (OCH_3), 39.5 (NCH_2CH), 36.0 ($NCOCH_2$), 32.4 ($CH(CH_3)_2$), 20.5 ($CHCH_3$), 20.0 ($CHCH_3$) and 17.5 (NCH_2CH); *m/z* (CI, NH_3) 212 ($M+H^+$, 100%), 180 (10); Found: $M+H^+$, 212.1285. $C_{11}H_{17}NO_3$ requires for $M+H^+$, 212.1287.

Radical cyclisation of methyl 2-(2,2-dichloro-N-(3-methyl-2-butenyl)ethanamido)propenoate (**30b**) *using 1.1 equivalents of tributyltin hydride*

Following the general procedure, alkene (**30b**) (131 mg, 0.47 mmol) was reacted with tributyltin hydride (150 mg, 0.52 mmol) and azobisisobutyronitrile (8 mg) in benzene (37 ml). Column chromatography (silica; petroleum ether-diethyl ether, 2:1) afforded *methyl (2R,S,4R,S)-(4-chloro-*N*-3-methyl-2-butenyl)pyroglutamate* (**33**) (43 mg, 38%) and *methyl 2-(3R,S-chloro-4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate* (**35**) (18 mg, 16%) as colourless oils.

*Methyl (2R,S,4R,S)-(4-chloro-*N*-3-methyl-2-butenyl)pyroglutamate* (**33**); R_f 0.37 (petroleum ether-diethyl ether, 1:2); υ_{max} (thin film) 2956 (s), 2923 (s), 1745 (s), 1713 (s), 1438 (m), 1259 (s), 1214 (s), 1170 (w), 1109 (m), 809 (s) and 732 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.98 (1H, t, *J*=8, C=CH), 4.38-4.25 (2H, m, NCHCH and CHCl), 4.10 (1H, dd, *J*=9 and 4, NCH), 3.76-3.65 (1H, m, NCHCH), 3.72 (3H, s, OCH_3), 2.85-2.73 (1H, m, NCHCH), 2.34 (1H, appt dt, *J*=15 and 4, NCHCH), 1.80 (3H, s, CCH_3) and 1.58 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 171.2, 169.8 (NCO and CO_2CH_3), 139.2 (C=CH), 117.1 (CH=C), 56.4 (NCH), 52.9 (CHCl), 52.7 (OCH_3), 40.1 (NCH_2), 33.8 ($NCHCH_2$), 25.7 (CCH_3), and 17.7 (CCH_3); *m/z* (CI, NH_3) 263 ($M^{35}+NH_4^+$, 15%), 246 ($M^{35}+H^+$, 100) and 210 (25); Found: $M^{35}+H^+$, 246.0892. $C_{11}H_{16}ClNO_3$ requires for $M^{35}+H^+$, 246.0897.

Methyl 2-(3R,S-chloro-4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate (**35**); R_f 0.45 (petroleum ether-diethyl ether, 1:2); υ_{max} (thin film) 2956 (s), 1738 (s), 1711 (s), 1629 (m), 1439 (w), 1369 (m) and 1213 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.19 (1H, s, C$\underline{H}$=C), 5.75 (1H, s, C$\underline{H}$=C), 3.81 (3H, s, OC$\underline{H}_3$), 3.73-3.42 (3H, m, NC$\underline{H}_2$ and C$\underline{H}$Cl), 2.51-2.43 (1H, m, NCHC$\underline{H}$), 1.91-1.88 (1H, m, C$\underline{H}$(CH_3)$_2$), 1.09 (3H, d, J=7, CHC$\underline{H}_3$) and 0.98 (3H, d, J=7, CHC$\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 169.6, 163.4 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 134.6 ($\underline{C}$=CH_2), 120.5 ($\underline{C}H_2$=C), 53.1 ($\underline{C}$HCl), 52.3 (O$\underline{C}H_3$), 45.7 ($NCH_2\underline{C}H$), 32.4 ($\underline{C}H(CH_3)_2$), 20.6 (CH$\underline{C}H_3$), 20.0 (CH$\underline{C}H_3$) and 17.5 (N$\underline{C}H_2$); *m/z* (CI, NH_3) 263 ($M^{35}+NH_4^+$, 15%), 246 ($M^{35}+H^+$, 100) and 210 (25); Found: $M^{35}+H^+$, 246.0891. $C_{11}H_{16}ClNO_3$ requires for $M^{35}+H^+$, 246.0897.

Radical cyclisation of methyl 2-(2,2-dichloro-N-(3-methyl-2-butenyl)ethanamido)propenoate (**30b**) *using 2.2 equivalents of tributyltin hydride*

Following the general procedure, alkene (**30b**) (145 mg, 0.52 mmol) was reacted with tributyltin hydride (166 mg, 0.57 mmol) and azobisisobutyronitrile (9 mg) in benzene (41 ml). After 3 h, a further equivalent of tributyltin hydride (166 mg, 0.57 mmol) and azobisisobutyronitrile (18 mg) in benzene (2 ml) was added and the solution heated at reflux for an additional 2 h. Column chromatography (silica; diethyl ether) afforded *methyl (2R,S)-(*N*-3-methyl-2-butenyl)pyroglutamate* (**31**) (50 mg, 46%) and *methyl 2-(4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate* (**32**) (12 mg, 11%) as colourless oils.

Radical cyclisation of methyl 2-(2,2,2-trichloro-N-(3-methyl-2-butenyl)ethanamido)propenoate (**30c**) *using 1.1 equivalents of tributyltin hydride*

Following the general procedure, alkene (**30c**) (100 mg, 0.32 mmol) was reacted with tributyltin hydride (102 mg, 0.35 mmol) and azobisisobutyronitrile (5 mg) in benzene (25 ml). Column chromatography (silica; petroleum ether-ethyl acetate, 3:1) afforded *methyl (2R,S)-(4,4-dichloro-*N*-3-methyl-2-butenyl)pyroglutamate* (**34**) (43 mg, 22%) and *methyl 2-(3,3-dichloro-4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate* (**36**) (18 mg, 23%) as colourless oils.

*Methyl (2R,S)-(4,4-dichloro-*N*-3-methyl-2-butenyl)pyroglutamate* (**34**); R_f 0.29 (petroleum ether-ethyl acetate, 3:1); υ_{max} (thin film) 2949 (s), 2923 (s), 1739 (s), 1697 (s), 1441 (m), 1412 (m), 1209 (s), 1170 (s), 1030 (w) and 989 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.03 (1H, t, J=7, C$\underline{H}$=C), 4.34 (1H, dd, J=15 and 6, NC$\underline{H}$CH), 4.15 (1H, dd, J=8 and 5, NC$\underline{H}$), 3.77-3.30 (1H, m, NC$\underline{H}$CH), 3.73 (3H, s, OC$\underline{H}_3$), 3.12 (1H, dd, J=15 and 8, NCHC$\underline{H}$), 3.01 (1H, dd, J=15 and 5, NCHC$\underline{H}$), 1.68 (3H, s, CC$\underline{H}_3$), and 1.58 (3H, s, CC$\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 169.9, 167.1 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 135.0 ($\underline{C}$=CH), 116.2 ($\underline{C}$H=C), 80.0 ($\underline{C}Cl_2$), 54.8 (N$\underline{C}$H), 52.9 (O$\underline{C}H_3$), 45.6 (N$\underline{C}H_2$), 40.7 (NCH$\underline{C}H_2$), 25.8 (C$\underline{C}H_3$) and 17.8 (C$\underline{C}H_3$); *m/z* (CI, NH_3) 280 ($M^{35}+H^+$, 80%), 244 (100), 212 (35), 202 (20) and 170 (10). Found: $M^{35}+H^+$, 280.0498. $C_{11}H_{15}Cl_2NO_3$ requires for $M^{35}+H^+$, 280.0507.

Methyl 2-(3,3-dichloro-4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate (**36**); R_f 0.17 (petroleum ether-ethyl acetate, 3:1); υ_{max} (thin film) 2949 (s), 2923 (s), 1732 (s), 1697 (s), 1440 (m), 1417 (m), 1213 (s), 1173 (s), 1028 (w) and 991 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.41 (1H, s, C$\underline{H}$=C), 5.95 (1H, s, C$\underline{H}$=C), 3.91 (3H, s, OC$\underline{H}_3$), 3.75 (1H, dd, J=10 and 7, NC$\underline{H}$CH), 3.49 (1H, appt t, J=10, NC$\underline{H}$CH), 2.58 (1H, m C$\underline{H}CH_3$), 2.32-2.21 (1H, m, $CH_2C\underline{H}$), 1.35 (3H, d, J=7, CHC$\underline{H}_3$) and 1.07 (3H, d, J=7, CHC$\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) 166.5, 162.9 (N$\underline{C}$O and $\underline{C}O_2CH_3$), 134.2 ($\underline{C}$=CH_2), 122.4 ($\underline{C}H_2$=C), 85.1 ($\underline{C}Cl_2$), 55.5 ($NCH_2\underline{C}H$), 52.7

($OC̲H_3$), 28.9 ($C̲HCH_3$), 20.7 ($CHC̲H_3$), 20.1 ($NC̲H_2$) and 17.5 ($CHC̲H_3$); *m/z* (CI, NH_3) 280 ($M^{35}+H^+$, 80%), 244 (100), 212 (35), 202 (20) and 170 (10). Found: $M^{35}+H^+$, 280.0499. $C_{11}H_{15}Cl_2NO_3$ requires for $M^{35}+H^+$, 280.0507.

Radical cyclisation of methyl 2-(2,2,2-trichloro-N-(3-methyl-2-butenyl)ethanamido)propenoate **(30c)** *using 3.3 equivalents of tributyltin hydride*

Following the general procedure, alkene (**30c**) (98 mg, 0.31 mmol) was reacted with tributyltin hydride (99 mg, 0.34 mmol) and azobisisobutyronitrile (5 mg) in benzene (24 ml). After 3 h, a further 2.2 equivalents of tributyltin hydride (198 mg, 0.68 mmol) and *bis*-azoisobutyronitrile (10 mg) in benzene (2 ml) was added and the solution heated at reflux for an additional 2 h. Column chromatography (silica; diethyl ether) afforded *methyl (2R,S)-(*N*-3-methyl-2-butenyl)pyroglutamate* (**31**) (18 mg, 27%) and *methyl 2-(4R,S-isopropyl-2-oxo-pyrrolidin-1-yl)acrylate* (**32**) (12 mg, 12%) as colourless oils.

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