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The Synthesis Of Substituted Pyrrolidines By A Samarium (II) Iodide-Mediated Ring Closure. Part 1

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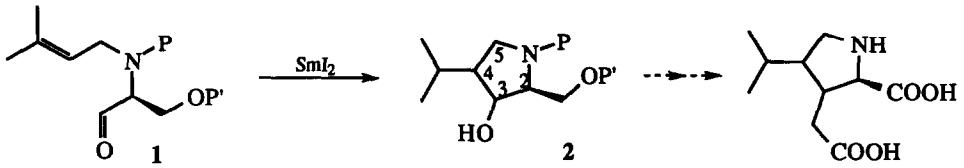
Abstract: Samarium (II) iodide-mediated ring closures, of substituted *N*-allyl derivatives of L-serine, have been used to generate a series of 2,3,4-trisubstituted pyrrolidine derivatives.

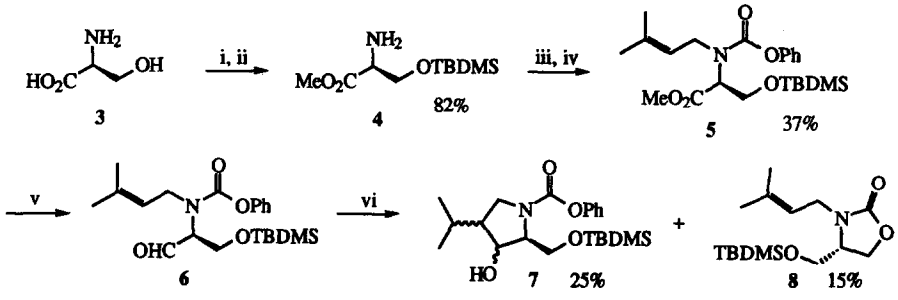
The usefulness of samarium iodide as a versatile reagent in organic synthesis has been demonstrated by its widespread application[1] for the reduction of a variety of functional groups,[2] as well as its mediation of a range of unusual reductive cyclisations[3] and intramolecular coupling reactions.[4] The oxophilic samarium(II) species, a potent reducing agent, induces reaction via two sequential one-electron reductions, and the intermediate radicals so formed are capable of undergoing a range of carbon-carbon bond-forming reactions. Using this approach, samarium iodide-mediated reactions have been used to generate a range of carbocycles[5] and heterocycles.[6] We report the extension of this reaction to the construction of 2,3,4-trisubstituted pyrrolidines (Scheme 1). These are potential precursors for the neurotoxic kainoid group of amino acids[7] and their analogues.



Scheme 1

The strategy envisaged using the α-aminoaldehyde **1**, prepared from L-serine, which would be reacted with samarium (II) to give substituted pyrrolidines **2** (Scheme 1). It was anticipated that this ring closure would be stereoselective, with the chiral centre at the C2 position influencing the newly-generated chiral centres at the C3 and C4 positions. Conversion of intermediate **2** to dihydrokainoids, using standard synthetic procedures, would then be expected to be straightforward.

Thus, L-serine **3** was converted to its methyl ester in quantitative yield by passing hydrogen chloride gas through a suspension of L-serine in dry methanol[9] (Scheme 2). The alcohol was then protected as a silyl ether by reaction with *tert*-butyldimethylsilyl chloride, triethylamine and 4-dimethylaminopyridine in dichloromethane. The crude **4**, obtained in 81% yield as a pale yellow oil, was converted directly to the carbamate **5** in 91% yield by reductive amination followed by *N*-protection. That this compound existed as two conformers was indicated by the ^{13}C n.m.r. spectrum, and is most probably due to restricted rotation about the N-CO bond. The ester functionality was then reduced using diisobutylaluminium hydride in toluene at -78°C; the crude aminoaldehyde **6** was obtained as a pale yellow oil which was shown by ^{1}H n.m.r. spectroscopy to be composed of a mixture of aldehyde and unreacted methyl ester in a ratio of 1:2, giving a 36% conversion to the aldehyde. The application of lithium aluminium hydride in the presence of excess diethylamine, which has been reported to reduce esters to give excellent yields of aldehydes,[10] resulted only in a moderate yield of the alcohol with no detectable aldehyde. Due to the propensity of α-aminoaldehydes such as **6** to racemise on silica gel,[11] the mixture was not purified further but used immediately.



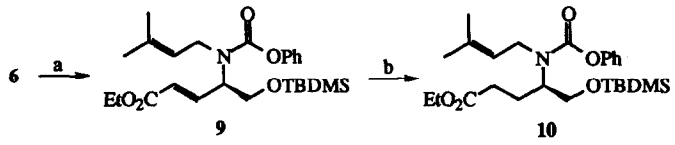
Reagents: (i) HCl, MeOH. (ii) TBDMSCl, Et_3N, DMAP, $PhCH_3$. (iii) 3-methyl-2-butenal, EtOAc, then $NaBH_4$, MeOH. (iv) PhOCOCl, $NaHCO_3$, H_2O, EtOAc. (v) DIBAL, $PhCH_3$, -78°C. (vi) $2SmI_2$, $^{t}BuOH$, HMPA, THF, 0°C.

Scheme 2

Treatment of aldehyde **6** with Sm (II) iodide (generated by the reaction of samarium metal powder with 1,2-diiodoethane in THF[13]) in HMPA/*tert*-butanol at 0°C, gave products **7** and **8**. Chromatography afforded pyrrolidine **7** in 25% yield and oxazolidinone **8** in 15% yield, both of which were obtained as colourless oils. The pyrrolidine **7** was shown by ^{1}H n.m.r. spectroscopy to be a mixture of all 4 possible diastereomers, although attempts to separate these by column chromatography or HPLC were unsuccessful. The oxazolidinone **8** arose by reduction of the aldehyde **6** by samarium (II) to give the corresponding alkoxide, followed by intramolecular nucleophilic attack of the alkoxide at the carbamate carbonyl. In view of the disappointing lack of stereocontrol observed in the cyclisation which was conducted at 0°C, the reaction was repeated at -78°C, but none of the desired cyclised product was obtained.

The α,β-unsaturated ester **9**, derived from aldehyde **6**, was prepared in 58% yield by the reaction of **6** with ethyl triphenylphosphoranylidene acetate (Scheme 3). The ethyl ester **9** was reacted with samarium (II) iodide solution and *tert*-butanol in THF under a nitrogen atmosphere for 18h. However, this did not give reductive cyclisation but instead afforded the saturated ethyl ester **10** in 48% yield. The reaction was repeated in the presence of the co-solvent HMPA, which has been reported to decrease the proportion of reduced versus

cyclised products,[13] but this only resulted in a lower yield of the reduced product, and recovery of starting material. Since only reduced product was obtained, it appeared that the α,β-unsaturated ester was not sufficiently reactive to be cyclised by samarium (II).

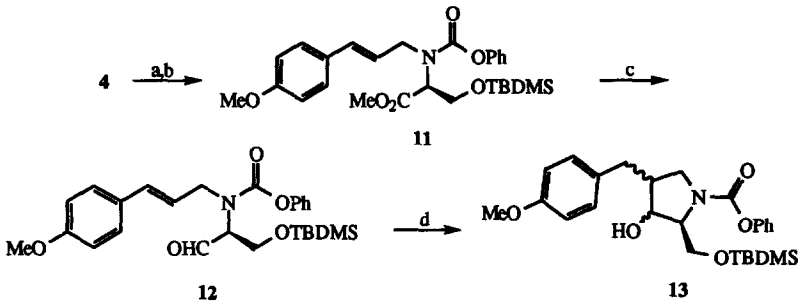


Reagents: a: $Ph_3P{=}CHCO_2Et$, DCM, 58%. b: $2SmI_2$, ^tBuOH, THF, 48%.

Scheme 3

In order to determine the range and reactivity of substituents amenable to radical cyclisation, an examination of substrates with a substituted cinnamyl side chain was undertaken.

The 4-methoxycinnamyl side chain was introduced into amine **4** by a reductive amination reaction as described above and the amine then protected as the *N*-phenyl carbamate **11** in 82% yield (Scheme 4). Once again the presence of two conformers was indicated by the fact that the carbon nuclei of the α-CH and the two CH_2 groups appeared as pairs of signals. The ester functionality was then reduced using diisobutylaluminium hydride in toluene at -78°C to give a pale yellow oil which comprised a mixture of the desired aldehyde **12** and unreacted methyl ester **11** in a ratio of 3:2, giving a yield of 56%; the α-aminoaldehyde was used without further purification. Aldehyde **12** was reacted with samarium iodide in the presence of HMPA at 0°C under the standard conditions. The discharge of the blue samarium (II) colour was more rapid than with the isoprenyl derivative and the reaction was complete after 30mins. Chromatography afforded pyrrolidine **13** in 44% yield, again as a mixture of several diastereomers, but all attempts to separate these by column chromatography or HPLC were unsuccessful. As anticipated, the cyclisation of **12** was both faster and of higher yield than **6**, consistent with the greater stability of the intermediate benzylic radical.[14]

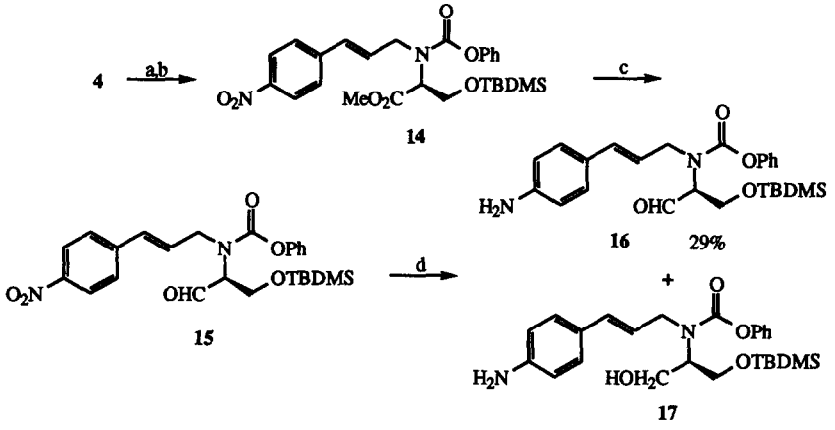


Reagents: a: 4-methoxycinnamaldehyde, EtOAc then $NaBH_4$, MeOH, 54%. b: PhOCOCl, $NaHCO_3$, H_2O, EtOAc, 82%. c: DIBAL, $PhCH_3$, -78°C, 56%. d: $2SmI_2$, ^tBuOH, HMPA, THF, 0°C, 44%.

Scheme 4

In order to ascertain if the nature of the substituents of the aromatic ring of the cinnamyl side chain had an effect on the reactivity of the double bond in the samarium (II) cyclisation reaction, the corresponding 4-nitro substituted compound was prepared. Thus, the silyl ether **4** was reacted with 4-nitrocinnamaldehyde in

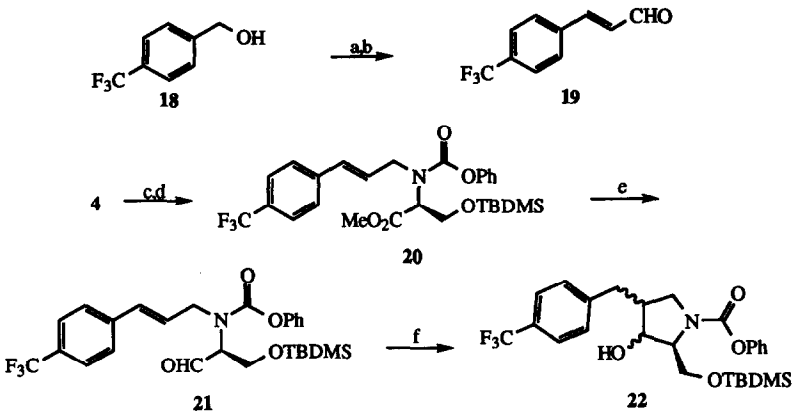
benzene, and converted to the *N*-phenyl carbamate **14**, as described above (Scheme 5). Reduction of the ester functionality using diisobutylaluminium hydride at -78°C gave a mixture of aldehyde **15** and unreacted methyl ester **14** in a ratio of 1:1. This mixture was not purified due to the instability of α-amino aldehydes. When aldehyde **15** was reacted with SmI_2, in the presence of HMPA at 0°C, under the standard conditions, the blue samarium (II) colour was discharged more rapidly than in previous reactions and 8 equivalents of the samarium reagent were required. The amine **16** was obtained in 29% yield, and although **17** could not be obtained pure its presence was inferred from the ^1H and ^{13}C n.m.r. spectra of the crude reaction product. The reduction of nitro to amino functional groups is a known reaction of samarium iodide[15] and must be taking place here faster than cyclisation, since no cyclised products were obtained.



Reagents: a: 4-Nitrocinnamaldehyde, EtOAc then $NaBH_4$, MeOH, 30%. b: PhOCOCl, $NaHCO_3$, H_2O, EtOAc, 77%. c: DIBAL, $PhCH_3$, -78°C, 49%. d: $8SmI_2$, ^tBuOH, HMPA, THF, 0°C.

Scheme 5

The cyclisation to a pyrrolidine derivative using a cinnamyl side chain which was substituted with an electron-withdrawing group which would be unaffected by the reducing conditions of the cyclisation reaction, was attempted as outlined in Scheme 6. 4-Trifluoromethylbenzyl alcohol **18** was treated with 2 equivalents of pyridinium chlorochromate in dichloromethane, giving a vigorous oxidation to the aldehyde which was obtained by distillation in 92% yield. Reaction with triphenylphosphoranylidene acetaldehyde gave the α,β-unsaturated aldehyde **19**, which could not be obtained free of the unhomologated aldehyde. The 4-trifluoromethylcinnamaldehyde **19** was reacted with protected L-serine **5** under standard reductive amination conditions, to give the monoalkylated product. Protection of the amine as the phenyl carbamate and reduction of the ester as described earlier, gave the pure α-aminoaldehyde **21**. The aldehyde **21** was reacted with SmI_2 under the standard conditions, the reaction proceeding at approximately the same rate as with the *p*-methoxy-derivative **12** as indicated by the time taken for the discharge of the blue colour of the reaction solution. The desired pyrrolidine **22** was obtained in 44% yield, again as a mixture of several diastereomers.



Reagents: a: PCC, DCM. b: Ph_3P=CH-CHO, $PhCH_3$. c: 4-trifluoromethylcinnamaldehyde, EtOAc then $NaBH_4$, MeOH, 54%. d: PhOCOCl, $NaHCO_3$, H_2O, EtOAc, 82%. e: DIBAL, $PhCH_3$, -78°C, 56%. f: $2SmI_2$, ^tBuOH, HMPA, THF, 0°C, 44%.

Scheme 6

These results demonstrate that the conjugatively activated olefins such as **12** and **21** cyclise faster and in higher yield than do unactivated olefins such as **6**. There was little or no observed diastereoselectivity in the three successful cyclisations.

EXPERIMENTAL

The 500 MHz ^1H NMR and 125 MHz ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) on a Bruker AM-500 (500MHz) spectrometer. Additional spectra were recorded on Varian Gemini 200 (200MHz) spectrometer. Chemical shifts (δ_H) are reported in parts per million (p.p.m.) and are referenced to the residual solvent peak (δ_H=7.27) or (δ_C=77.0). Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. Two dimensional COSY spectra were recorded on Varian Gemini 200 (200MHz) and Bruker AM-500 (500MHz) spectrometers, and nuclear Overhauser experiments recorded on the Bruker AM-500 (500MHz) spectrometer. Infra-red spectra were recorded as nujol mulls, thin films or in $CHCl_3$ solution using a Perkin-Elmer 1750 FT spectrometer. Only selected peaks are reported and absorption maxima (in cm^{-1}) are described as strong (s), medium (m), weak (w) or broad (br). Low resolution mass spectra (m/z) were recorded on VG Micromass ZAB 1F and VG Masslab 20-250 spectrometers using ammonia desorption chemical ionisation (DCI), chemical ionisation (CI) or positive argon fast atom bombardment (FAB) techniques. Gas Chromatography Mass Spectra (GCMS) were recorded on a VG Trio-1 spectrometer. Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a VG ZAB-E instrument by manual peak matching, and were conducted by Dr. J.A. Ballantine at University College of Swansea. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, using a path length of 1 dm, with concentrations (c) given in g/100 cm^3, and solvent and temperature as recorded. Microanalyses were performed by the microanalytical service of the Dyson Perrins Laboratory. Melting points were recorded on a

Stuart Scientific SMP1 melting point device and are uncorrected. Thin layer chromatography (t.l.c.) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60 F_{254}. Plates were visualised using uv light (254 and 366nm), iodine vapour, a solution of 5% w/v *dodeca*-molybdophosphoric acid in EtOH or a solution of ninhydrin in methanol. Flash column chromatography was carried out using Sorbsil™ C_{60} H(40-60 mm) silica gel. Solvents were distilled prior to use using standard literature procedures. THF was distilled from sodium/benzophenone under nitrogen prior to use.

Methyl (2S)-2-amino-3-[(*tert*-butyldimethylsilyl)oxy] propionate (4). Through a solution of L-serine (5g, 48mmol) in methanol (25ml) was passed hydrogen chloride gas until the solution was saturated. The flask was stored overnight at 0°C, after which the solvent was removed *in vacuo*, affording white crystals of L-serine methyl ester hydrochloride (7.40g, 100%).[9]

L-serine methyl ester hydrochloride (7.40g, 47.6mmol) was stirred with triethylamine (22ml) in dichloromethane (150ml) for 1h. A catalytic amount of dimethylaminopyridine was added, followed by *tert*-butyldimethylchlorosilane (8.24g, 54.8mmol) and the solution stirred at r.t. for 4h. A saturated solution of aqueous sodium bicarbonate (100ml) was then added and the organic layer separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude silyl ether[9] **4** (9.0g); Rf 0.24 (ethyl acetate:dichloromethane, 5:2); ν_{max} (thin film) 3500-3150 (w), 3020-2840 (s), 1745 (s), 1680 (w), 1600 (w), 1470 (s), 1440 (m), 1390 (m), 1360 (m), 1255 (s), 1225-1150 (s), 1100 (s), 1050 (s), 1010 (m), 940 (m) and 890 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 4.00-3.78 (2H, ddd, J_1 9.4Hz, J_2 4.0Hz, J_3 3.6Hz, C$\underline{H}_2$OSi), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.53 (1H, t, J 3.6Hz, NC$\underline{H}$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$) and 0.06 (6H, s, 2 x Si-C$\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 174.8 ($\underline{C}O_2CH_3$), 65.3 ($\underline{C}H_2OSi$), 56.4 (N-$\underline{C}$H), 25.5 (Si-C($\underline{C}H_3$)$_3$), 17.9 (Si-$\underline{C}$(CH$_3$)$_3$) and -5.8 (Si-$\underline{C}H_3$).

Methyl (2S)-2-[(3-methyl-2-butenyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate. To a solution of **4** (4.9g) in benzene (10ml) was added 3-methyl-2-butenal (1.05g, 12.6mmol) dropwise while stirring at r.t.. After 0.6h ethyl acetate was added and the solution dried ($MgSO_4$) and concentrated *in vacuo*. The crude imine was dissolved in methanol (20ml) and sodium borohydride (0.82g, 19.1mmol) added portionwise at 0°C. After 0.2h the ice bath was removed and stirring continued for 3h. Water and ethyl acetate were then added and the organic layer separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded the title compound[9] as a pale yellow oil (3.46g, 44% from hydrochloride salt): Rf 0.36 (hexane-ethyl acetate, 4:1); ν_{max} (thin film) 3400-3300 (w), 3000-2840 (s), 1760-1730 (s), 1470 (m), 1435 (m), 1385 (w), 1365 (w), 1255 (s), 1205 (s), 1175 (m), 1155 (m), 1110 (s), 1050 (w), 1005 (w), 985 (w), 940 (w) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 5.20 (1H, dd, J_1 6.9Hz, J_2 5.9Hz, C$\underline{H}$=C), 3.87-3.73 (2H, m, C$\underline{H}_2$OSi), 3.70 (3H, s, $CO_2C\underline{H}_3$), 3.35 (1H, t, J 4.9Hz, N-C$\underline{H}$), 3.30-3.05 (2H, m, C$\underline{H}_2$-C=), 1.69 (3H, s, C$\underline{H}_3$-C=), 1.60 (3H, s, C$\underline{H}_3$-C=), 0.84 (9H, s, Si-C(C$\underline{H}_3$)$_3$) and 0.01 (6H, s, 2 x Si-C$\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 173.89 ($\underline{C}O_2CH_3$), 134.97 ($\underline{C}$=), 122.35 ($\underline{C}$H=), 64.43 ($\underline{C}H_2OSi$), 62.30 (N-$\underline{C}$H), 51.56 ($CO_2\underline{C}H_3$), 45.28 (N-$\underline{C}H_2$), 25.65 (Si-C($\underline{C}H_3$)$_3$), 18.10 ($\underline{C}H_3$-C=), 17.72 ($\underline{C}H_3$-C=) and -5.58, -5.67 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 302 ($M+H^+$, 100%).

Methyl (2S)-2-[(3-methyl-2-butenyl)(phenyloxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (5). To a solution of the previous compound (1.76g, 5.85mmol) in ethyl acetate (40ml) was added a

saturated aqueous solution of sodium bicarbonate (6ml) at 0°C while stirring, followed by the addition of phenyl chloroformate (0.75ml, 0.95g, 5.85mmol). After 1h water was added and the solution allowed to reach r.t.. The organic layer was then separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded the carbamate **5** as a colourless oil (2.24g, 91%); Rf 0.43 (hexane-ethyl acetate, 4:1); $[\alpha]_D^{19}$ +17.4° (c 0.98, $CHCl_3$), lit. +17° (c 0.06, $CHCl_3$)[9]; ν_{max} (thin film) 3100-2820 (s), 1780-1690 (s), 1595 (w), 1495 (w), 1480-1400 (m), 1386 (m), 1255 (m), 1210 (s), 1160 (s), 1120 (m), 1070 (m), 1005 (m), 935 (m), 915 (m) and 840 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.40-7.05 (5H, m, ArH), 5.37 (1H, m, C<u>H</u>=C), 4.52-3.92 (5H, m, $C\underline{H}_2$-N, $C\underline{H}_2OSi$ and N-C<u>H</u>), 3.74 (3H, s, $CO_2C\underline{H}_3$), 1.76 (3H, s, $C\underline{H}_3$-C=), 1.69 (3H, s, $C\underline{H}_3$-C=), 0.92 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.10 (6H, s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 170.39, 170.22 ($\underline{C}O_2CH_3$), 154.83, 154.35, 151.55, 151.30, 135.92, 129.96, 129.34, 125.36, 121.78, 121.65, 121.19, 120.48, 120.35 (ArC), 61.99, 61.38, 61.10 (N-<u>C</u>H and $\underline{C}H_2OSi$), 52.12, 52.02 ($CO_2\underline{C}H_3$), 46.30, 45.98 (=C-$\underline{C}H_2$-N), 25.65, 25.38 (Si-C($\underline{C}H_3$)$_3$), 18.00, 17.65 ($\underline{C}H_3$-C=) and -5.74 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 422 ($M+H^+$, 60%), 364 (22) and 354 (100).

(2S)-2-[(3-Methyl-2-butenyl)(phenyloxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propanal (6). To a solution of **5** (1.00g, 2.38mmol) in dry toluene (25ml) was added diisobutylaluminium hydride (2.5ml, 1.5M, 3.83mmol) dropwise while stirring at -78°C under a nitrogen atmosphere. After 2h methanol (0.5ml) was added dropwise to quench the reaction followed by saturated aqueous Rochelle salt solution to stabilize the complex. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude aminoaldehyde as a pale yellow liquid (0.84g (40% pure by ^1H nmr), 36%); Rf 0.60 (hexane-ethyl acetate, 4:1); δ_H (200MHz, $CDCl_3$) 9.69 (1H, d, CH-C<u>H</u>O), 7.43-7.05 (5H, m, ArH), 5.43-5.29 (1H, m, C<u>H</u>=C), 4.54-3.90 (5H, m, $C\underline{H}_2$-N, $C\underline{H}_2OSi$ and N-C<u>H</u>), 1.84-1.69 (6H, m, 2 x $C\underline{H}_3$-C=), 0.93 (9H, s, Si-($C\underline{H}_3$)$_3$) and 0.11 (6H, s, 2 x Si-$C\underline{H}_3$).

Preparation of Samarium (II) Iodide.[13] Samarium metal (3.0g, 20mmol) was placed in a reaction flask fitted with a dropping funnel containing 1,2-diiodoethane (2.82g, 10mmol) in THF (100ml). The THF solution was added over 30min to the stirred solution, which was then stirred for 18h. The initial green colour changes to a deep blue-green solution of samarium (II) iodide (0.1M).

Cyclisation of (6) with Samarium (II) Iodide. 6 (0.45g, 40% by ^1H nmr) was dissolved in dry degassed tetrahydrofuran (25ml) and stirred at 0°C. To the solution was added HMPA (1.25ml) and *tert*-butanol (0.17g, 2.27mmol, 2 equivalents). Samarium (II) iodide solution (35ml, 0.1M, 3.5mmol) was added dropwise over 10mins. The solution was stirred at 0°C for 18h and then passed through silica to remove samarium salts. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded pyrrolidine **7** (0.039g, 21%) as an inseparable mixture of diastereomers and oxazolidinone **8** (0.028g, 15%), both of which were colourless oils:

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-hydroxy-4-(isopropyl) pyrrolidine (7). Rf 0.74 (ethyl acetate); ν_{max} ($CDCl_3$) 3700-3300 (w), 3000-2840 (m), 1710 (s), 1495 (w), 1465 (w), 1400 (s), 1255 (w), 1205 (s), 1160 (w), 1130-1040 (m) and 900 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.43-7.07 (5H, m, ArH), 4.98 (1H, m, C<u>H</u>OH), 4.5-3.0 (8H, m, N-$C\underline{H}_2$, N-C<u>H</u>, $C\underline{H}_2OSi$, C<u>H</u>OH, C<u>H</u>-CH(CH_3)$_2$ and CH-C<u>H</u>(CH_3)$_2$), 1.83 (6H, s, CH($C\underline{H}_3$)$_2$), 0.92 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.09 (6H, s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 129.43, 125.46, 121.87, 121.67 (ArC), 113.44, 76.00 (<u>C</u>HOH), 64.54, 62.29 ($\underline{C}H_2OSi$ and N-<u>C</u>H),

51.31, 50.39, 49.36, 49.26 (N-$\underline{C}H_2$), 29.41, 25.73 (Si-C($\underline{C}H_3$)$_3$, 20.10 ($\underline{C}H_3$-C=) and -5.67 (Si-CH_3); m/z (DCI, NH_3) 392 ($M+H^+$, 15%), 376 (28) and 124 (100).

(4S)-*N*-(3-Methyl-2-butenyl)-4-[(*tert*-butyldimethylsilyl)oxymethyl]-2-oxazolidinone (8). Rf 0.88 (ethyl acetate); δ_H (200MHz, $CDCl_3$) 5.19 (1H, t, J 7Hz, C=C$\underline{H}$), 4.37-4.02 (4H, m, N-CH_2 and CH_2OSi), 3.87-3.70 (1H, m, N-C$\underline{H}$), 3.64 (2H, d, J 4Hz, $\underline{C}H_2$-OCO), 1.75 (3H, s, C=C-$\underline{C}H_3$), 1.71 (3H, s, C=C-$\underline{C}H_3$), 0.92 (9H, s, Si-C($\underline{C}H_3$)$_3$) and 0.09 (6H, s, 2 x Si-$\underline{C}H_3$); m/z (DCI, NH_3) 300 ($M+H^+$, 100%), 244 (5), 191 (3) and 174 (14).

Ethyl (4R)-4-[(3-methyl-2-butenyl)(phenyloxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-enoate (9). The crude aminoaldehyde **6** (0.50g) was dissolved in dichloromethane (12ml) and ethyl (triphenylphosphoranylidene) acetate (0.74g, 2.08mmol) added portionwise while stirring. The solution was allowed to stir at r.t. for 1h and the solvent then removed *in vacuo*. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded **9** as a colourless liquid (0.344g, 58%); Rf 0.42 (hexane-ethyl acetate, 4:1); ν_{max} ($CDCl_3$) 3020-2850 (m), 1740-1700 (s), 1595 (w), 1500 (w), 1470 (m), 1410 (m), 1370 (m), 1320 (m), 1255 (s), 1205 (s), 1115 (m), 1045 (m), 985 (w) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.45-7.04 (5H, m, ArH), 7.00 (1H, m, CO-CH=C$\underline{H}$), 6.01 (1H, d, J 16Hz, CO-C$\underline{H}$=CH), 5.32 (1H, m, C$\underline{H}$=C), 4.63 (1H, m, N-C$\underline{H}$), 4.28-3.82 (6H, m, N-$\underline{C}H_2$, $\underline{C}H_2$OSi and CH_3-$\underline{C}H_2$-O), 1.74 (3H, s, =C-$\underline{C}H_3$), 1.69 (3H, s, =C-$\underline{C}H_3$), 1.29 (3H, m, $\underline{C}H_3$-CH_2-O), 0.93 (9H, s, Si-C($\underline{C}H_3$)$_3$) and 0.10 (6H, s, 2 x Si-$\underline{C}H_3$); δ_C (50.3MHz, $CDCl_3$) 166.41 (=CH-$\underline{C}O_2$), 154.13 (N-$\underline{C}O_2$), 144.02, 142.90, 138.43, 129.43, 125.72, 125.48, 123.39, 123.31, 121.90, 121.53, 121.40, 120.84 ($\underline{C}$=), 62.85, 62.75, 60.56, 59.87, 59.72 (N-$\underline{C}$H and $\underline{C}H_2$OSi), 44.73 (N-$\underline{C}H_2$), 32.69, 25.67, 25.52 (Si-C($\underline{C}H_3$)$_3$), 17.74 (=C-$\underline{C}H_3$), 14.07 ($\underline{C}H_3$-CH_2-O) and -5.64 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 462 ($M+H^+$, 8%), 206 (100) and 94 (42).

Ethyl (4R)-4-[*N*-(3-methyl-2-butenyl)(phenyloxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy] pentanoate (10). The ethyl ester **9** (0.15g, 0.33mmol) was dissolved in dry degassed tetrahydrofuran (12ml) and stirred at r.t. under nitrogen. Samarium (II) iodide solution (10ml, 0.1M, 1mmol) was added dropwise over 10mins, followed by the addition of *tert*-butanol (0.050g, 0.65mmol, 2 equivalents). The solution was stirred for 18h, filtered through silica and concentrated *in vacuo*. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded **10** as a pale yellow liquid (0.073g, 48%): Rf 0.39 (hexane-ethyl acetate, 4:1); ν_{max} ($CHCl_3$) 2957-2858 (m), 1723 (s), 1596 (w), 1414 (m), 1253 (s), 1207 (s), 1163 (s), 839 (s) and 781 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.41-7.09 (5H, m, ArH), 5.32 (1H, m, C$\underline{H}$=C), 4.25-3.64 (7H, m, N-$\underline{C}H_2$, $\underline{C}H_2$OSi, CH_3-$\underline{C}H_2$-O and N-C$\underline{H}$), 2.40 (2H, m, $\underline{C}H_2$-CO_2), 1.96 (2H, m, $\underline{C}H_2$-CH_2-CO_2), 1.74 (3H, s, =C-$\underline{C}H_3$), 1.69 (3H, s, =C-$\underline{C}H_3$), 1.27 (3H, m, CH_2-$\underline{C}H_3$), 0.92 (9H, s, Si-C($\underline{C}H_3$)$_3$) and 0.08 (6H, s, 2 x Si-$\underline{C}H_3$); δ_C (50.3MHz, $CDCl_3$) 173.62 ($\underline{C}O_2$-CH_2), 151.71, 134.31, 129.37, 125.25, 121.94, 121.62, 121.39 (ArC), 79.39, 69.97, 64.37, 63.37, 63.98, 60.46, 58.90 (N-$\underline{C}$H and $\underline{C}H_2$OSi), 44.00 (N-$\underline{C}H_2$), 31.14, 30.97, 25.74, 25.61 (Si-C($\underline{C}H_3$)$_3$), 23.80, 18.05, 17,72 (=C-$\underline{C}H_3$), 14.06 ($\underline{C}H_3$-CH_2-O) and -5.67 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 464 ($M+H^+$, 9%), 396 (7), 370 (6), 206 (100) and 94 (42).

Methyl (2S)-2-[[3-(4-methoxyphenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate To a solution of **4** (4.0g) in benzene (15ml) was added 4-methoxycinnamaldehyde (2.78g, 17.2mmol) portionwise over 0.25h while stirring at r.t.. After 1h ethyl acetate was added and the solution dried

($MgSO_4$) and concentrated *in vacuo*. The crude imine was dissolved in methanol (16ml) and sodium borohydride (1.09g, 26.1mmol) added portionwise over 0.5h at 0°C. After 0.2h the ice bath was removed and stirring continued for 0.5h. Water and ethyl acetate were then added and the organic layer separated,washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (dichloromethane-ethyl acetate, 19:1) afforded the title compound as a colourless oil (3.51g, 54%); Rf 0.55 (dichloromethane-ethyl acetate, 9:1); (Found: C, 63.09; H, 8.90; N, 3.38. $C_{20}H_{33}NO_4Si$ requires C, 63.29; H, 8.76; N, 3.69%); ν_{max} (liquid film) 3400-3200 (w), 2970-2820 (s), 1760-1730 (s), 1610 (s), 1510 (s), 1465 (s), 1390 (m), 1360 (m), 1300 (m), 1250 (s), 1175 (s), 1110 (s), 1040 (s), 970 (m) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.30 (2H, d, J 9Hz, ArH), 6.84 (2H, d, J 9Hz, ArH), 6.46 (1H, d, 16Hz, CH=C<u>H</u>-Ar), 6.11 (1H, dt, J_1 16Hz, J_2 6.5Hz, C<u>H</u>=CH-Ar), 3.85 (2H, m, $C\underline{H}_2OSi$), 3.79 (3H, s, -$OC\underline{H}_3$), 3.71 (3H, s, -$OC\underline{H}_3$), 3.43 (1H, t, 5Hz, N-C<u>H</u>), 3.54-3.26 (2H, dq, J_1 14.5Hz, J_2 6.5Hz, N-$C\underline{H}_2$), 0.87 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.03 (6H, s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 174.09 ($\underline{C}O_2CH_3$), 159.26 (<u>C</u>-OMe), 131.43 (CH=<u>C</u>H-Ar), 129.90 (<u>C</u>-CH=CH), 127.57 (ArC, *m* to -OMe), 125.75 (<u>C</u>H=CH-Ar), 113.99 (ArC, *o* to -OMe), 64.48 (N-<u>C</u>H), 62.08 ($\underline{C}H_2OSi$), 55.16 (-O<u>C</u>H_3), 51.65 (-O<u>C</u>H_3), 50.10 (N-<u>C</u>H_2), 25.58 (Si-C(<u>C</u>H_3)$_3$), 18.00 (Si-<u>C</u>(CH_3)$_3$) and -5.75, -5.85 (Si-CH_3); m/z (DCI, NH_3) 380 ($M+H^+$, 6%), 162 (20) and 147 (100).

Methyl (2S)-2-[(phenoxycarbonyl)-[3-([4-methoxyphenyl]prop-2-en-1-yl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (11). To a solution of the previous compound (2.97g, 7.80mmol) in ethyl acetate (50ml) was added a saturated aqueous solution of sodium bicarbonate (8ml) at 0°C while stirring, followed by the addition of phenyl chloroformate (1.22g, 7.80mmol). After 1h water was added and the solution allowed to reach r.t.. The organic layer was then separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded **11** as a colourless oil (3.20g, 82%); Rf 0.39 (hexane-ethyl acetate, 4:1); (Found: C, 64.52; H, 7.30; N, 2.60. $C_{27}H_{37}NO_6Si$ requires C, 64.93; H, 7.41; N, 2.81%); ν_{max} (liquid film) 3080-2810 (m), 1760-1710 (s), 1600 (m), 1510 (m), 1455 (s), 1410 (s), 1250 (s), 1120 (s), 1070 (s), 1040 (m), 1005 (m), 970 (m), 935 (w), 915 (m) and 835 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.45-7.10 (7H, m, ArH), 6.90 (2H, d, J 9Hz, ArH), 6.68-6.53 (1H, m, CH=C<u>H</u>-Ar), 6.36-6.18 (1H, dt, J_1 16Hz, J_2 7Hz, C<u>H</u>=CH-Ar), 4.70-4.48 (2H, m, N-$C\underline{H}_2$), 4.32-4.11 (3H, m, N-C<u>H</u> and $C\underline{H}_2OSi$), 3.83 (3H, s, -$OC\underline{H}_3$), 3.76 (3H, s, -$OC\underline{H}_3$), 0.96 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.13 (6H, s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 170.20 ($\underline{C}O_2CH_3$), 159.57, 155.02, 132.82, 131.89, 129.49, 127.80, 125.59, 123.85, 123.12, 121.93, 121.75, 114.15 (<u>C</u>=), 61.95, 61.62, 61.34, 61.15 (N-<u>C</u>H and $\underline{C}H_2OSi$), 55.26 (-O<u>C</u>H_3), 52.17 (-O<u>C</u>H_3), 50.76, 50.05 (N-<u>C</u>H_2), 25.74 (Si-C(<u>C</u>H_3)$_3$), 18.07 (Si-<u>C</u>(CH_3)$_3$) and -5.61 (Si-<u>C</u>H_3); m/z (DCI, NH_3) 500 ($M+H^+$, 15%), 354 (25), 260 (14) and 147 (100).

(2S)-2-[(Phenoxycarbonyl)-[3-(4-methoxyphenyl)(prop-2-en-1-yl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propanal (12). To a solution of the methyl ester **11** (1.00g, 2.00mmol) in dry toluene (20ml) was added diisobutylaluminium hydride (1.95ml, 1.5M, 2.92mmol) dropwise while stirring at -78°C under a nitrogen atmosphere. After 5h methanol (0.5ml) was added dropwise to quench the reaction followed by saturated aqueous Rochelle salt solution to stabilize the complex. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **12** as a pale yellow liquid (0.88g (60% aldehyde by nmr), 56%); δ_H (200MHz, $CDCl_3$) 9.74 (1H, m, CH-C<u>H</u>O), 7.48-6.83 (9H, m, ArH), 6.67-6.52 (1H, m, Ar-

CH=C<u>H</u>), 6.30-6.11 (1H, m, Ar-C<u>H</u>=CH), 4.73-4.59 (1H, m, N-C<u>H</u>), 4.38-4.05 (4H, m, N-C<u>H</u>$_2$ and C<u>H</u>$_2$OSi), 3.83 (3H, s, Ar-OC<u>H</u>$_3$), 0.96 (9H, s, Si-(C<u>H</u>$_3$)$_3$) and 0.13 (6H, s, 2 x Si-C<u>H</u>$_3$).

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-hydroxy-4-(4-methoxybenzyl) pyrrolidine (13). The crude aminoaldehyde **12** (0.42g, 60%) was dissolved in dry degassed tetrahydrofuran (60ml) and stirred at 0°C. To the solution was added HMPA (3ml) and *tert*-butanol (0.125g, 2 equivalents). Samarium (II) iodide solution (17ml, 0.1M, 1.7mmol) was added dropwise over 2mins. The solution was stirred at 0°C for 30min, quenched with aqueous sodium bicarbonate solution and then passed through silica to remove samarium salts. Chromatography on silica (hexane-ethyl acetate, 4:1 to 1:1) afforded pyrrolidine **13** (0.112g, 44%) as a colourless solid which was shown to be an inseparable mixture of diastereomers: Rf 0.34 (hexane:ethyl acetate, 3:2); ν_{max} ($CDCl_3$) 3580 (br w), 2960-2820 (m), 1720 (s), 1610 (m), 1515 (s), 1495 (m), 1470 (m), 1395 (s), 1255 (s), 1205 (s), 1165 (m), 1095 (m), 1070 (m) and 1040 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.40-6.90 (9H, m, ArH), 4.05-3.25 (9H, m, N-C<u>H</u>, C<u>H</u>$_2$OSi, C<u>H</u>$_2$Ar, C<u>H</u>OH and-OC<u>H</u>$_3$), 3.0-2.5 (2H, m, N-C<u>H</u>$_2$), 2.3-1.6 (1H, m, C<u>H</u>CH$_2$Ar), 0.82-0.79 (9H, m, Si-C(C<u>H</u>$_3$)$_3$) and -0.02- -0.04 (6H, m, Si-C<u>H</u>$_3$); δ_C (125.7MHz, $CDCl_3$) 159.11, 159.01 (<u>C</u>=O), 151.49, 151.40 (N-<u>C</u>O$_2$), 131.77, 129.56, 129.23, 129.13, 125.12, 125.09, 121.70, 121.54, 114.38, 113.63 (ArC and C=<u>C</u>), 71.35, 70.05, 66.47, 64.56, 62.18 (N-<u>C</u>H and <u>C</u>H$_2$OSi), 55.23, 55.09 (-O<u>C</u>H$_3$), 52.33, 51.27, 50.29, 49.79, 48.15, 46.40, 45.46, 34.26, 32.07, 29.67, 28.81 (-O<u>C</u>H$_3$ and N-<u>C</u>H$_2$), 25.95, 25.87, 23.49, 22.01 (Si-C(<u>C</u>H$_3$)$_3$), 20.63, 19.21, 19.00, 18.20, 18.12 (Si-<u>C</u>(CH$_3$)$_3$), 16.78, -5.40, -5.49 and -5.60 (Si-<u>C</u>H$_3$); m/z (DCI, NH_3) 472 ($M+H^+$, 44%), 452 (12), 414 (43), 378 (27), 147 (82) and 121 (100).

Methyl (2S)-2-[[3-(4-nitrophenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate. To a solution of **4** (2.0g) in benzene (7.5ml) was added 4-nitrocinnamaldehyde (1.52g, 8.58mmol) portionwise over 0.25h while stirring at r.t.. After 1h ethyl acetate was added and the solution dried ($MgSO_4$) and concentrated *in vacuo*. The crude imine was dissolved in methanol (8ml) and sodium borohydride (0.54g, 13.0mmol) added portionwise over 0.5h at 0°C. After 0.2h the ice bath was removed and stirring continued for 0.5h. Water and ethyl acetate were then added and the organic layer separated,washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (dichloromethane-ethyl acetate, 19:1) afforded the title compound as a colourless oil (1.01g, 30%); Rf 0.52 (hexane:ethyl acetate, 4:1); ν_{max} (liquid film) 3400-3300 (w), 2960-2820 (s), 1740 (s), 1655 (m), 1595 (s), 1470 (s), 1345 (s), 1255 (s), 1110 (s), 975 (m) and 840 (s); δ_H (200MHz, $CDCl_3$) 8.19-8.15 (2H, d, J 9Hz, ArH), 7.51-7.47 (2H, d, J 9Hz, ArH), 6.67-6.59 (1H, d, 16Hz, CH=C<u>H</u>-Ar), 6.52-6.38 (1H, dt, J_1 16Hz, J_2 5.6Hz, C<u>H</u>=CH-Ar), 3.96-3.80 (2H, m, C<u>H</u>$_2$OSi), 3.73 (3H, s, -OC<u>H</u>$_3$), 3.65-3.32 (2H, m, N-C<u>H</u>$_2$), 3.43 (1H, t, J 4.5Hz, N-C<u>H</u>), 2.04 (1H, s, N<u>H</u>), 0.91 and 0.87 (9H, 2 x s, Si-C(C<u>H</u>$_3$)$_3$) and 0.09, 0.04 (6H, 2 x s, 2 x Si-C<u>H</u>$_3$); δ_C (50.3MHz, $CDCl_3$) 173.82 (<u>C</u>O$_2$CH$_3$), 143.70 (<u>C</u>-NO$_2$), 133.47 (CH=<u>C</u>H-Ar), 129.47 (<u>C</u>H=CHAr), 126.89 (ArC, *m* to -NO$_2$), 124.08 (ArC *o* to -NO$_2$), 64.50 (N-<u>C</u>H), 62.27 (<u>C</u>H$_2$OSi), 51.74 (CO$_2$<u>C</u>H$_3$), 49.73 (N-<u>C</u>H$_2$), 25.55 (Si-C(<u>C</u>H$_3$)$_3$), 17.98 (Si-<u>C</u>(CH$_3$)$_3$) and -3.81, -5.75 (Si-<u>C</u>H$_3$); m/z (DCI, NH_3) 395 ($M+H^+$, 3%), 234 (36) and 132 (100).

Methyl (2S)-2-[(phenoxycarbonyl)-[3-(4-nitrophenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (14). To a solution of the previous compound (0.93g, 2.44mmol) in ethyl acetate (20ml) was added a saturated aqueous solution of sodium bicarbonate (2.5ml) at 0°C while stirring,

followed by the addition of phenyl chloroformate (0.38g, 2.44mmol). After 1h water was added and the solution allowed to reach r.t.. The organic layer was then separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (dichloromethane-ethyl acetate, 19:1) afforded **14** as a colourless oil (0.96g, 77%); Rf 0.74 (dichloromethane-ethyl acetate, 19:1); (Found: C, 60.57; H, 6.79; N, 5.39. $C_{26}H_{34}N_2O_7Si$ requires C, 60.70; H, 6.61; N, 5.45%); ν_{max} (liquid film) 2955-2860 (s), 1720 (s), 1600 (s), 1520 (m), 1495 (m), 1455 (s), 1410 (s), 1345 (m), 1260 (s), 1200 (s), 1110 (s), 910 (m) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 8.22-8.12 (2H, m, ArH), 7.55-7.49 (2H, m, ArH), 7.40-7.33 (2H, m, ArH), 7.27-7.16 (1H, m, ArH), 7.12-7.08 (2H, d, J 9Hz, ArH), 6.80-6.48 (2H, m, CH=C<u>H</u>-Ar and C<u>H</u>=CH-Ar), 4.75-4.47 (2H, m, N-C<u>H</u>$_2$), 4.37-4.10 (3H, m, N-C<u>H</u> and C<u>H</u>$_2$OSi), 3.77 (3H, s, -OC<u>H</u>$_3$), 0.91 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.10 (6H, s, 2 x Si-C<u>H</u>$_3$); δ_C (50.3MHz, $CDCl_3$) 169.95 (<u>C</u>O$_2$CH$_3$), 147.12, 143.48 (ArC-NO$_2$), 131.72, 130.93, 130.39, 129.64, 129.47, 126.99, 125.69, 124.18, 121.71 (ArC and =<u>C</u>), 61.80, 61.55 (N-<u>C</u>H and <u>C</u>H$_2$OSi), 52.33, 52.22 (CO$_2$<u>C</u>H$_3$), 50.05, 49.49 (N-<u>C</u>H$_2$), 25.62 (Si-C(<u>C</u>H$_3$)$_3$), 17.95 (Si-<u>C</u>(CH$_3$)$_3$) and -5.71 (Si-CH$_3$); m/z (DCI, NH_3) 515 ($M+H^+$, 100%), 457 (16), 383 (12) and 132 (64).

Methyl (2S)-2-[(phenoxycarbonyl)-[3-(4-nitrophenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propanal (15). To a solution of the methyl ester **14** (0.89g, 1.74mmol) in dry toluene (17ml) was added diisobutylaluminium hydride (1.69ml, 1.5M, 2.54mmol) dropwise while stirring at -78°C under a nitrogen atmosphere. After 5h methanol (0.5ml) was added dropwise to quench the reaction followed by saturated aqueous Rochelle salt solution to stabilize the complex. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **15** as a pale yellow liquid (0.82g (50% aldehyde by ^1H nmr), 49%); δ_H (200MHz, $CDCl_3$) 9.80 and 9.72 (1H, 2 x s, CH-CHO).

Attempted Cyclisation of (15) with Samarium (II) Iodide. 15 (0.89g, 50%) was dissolved in dry degassed tetrahydrofuran (100ml) and stirred at 0°C. To the solution was added HMPA (5ml) and *tert*-butanol (0.195g, 2 equivalents). Samarium (II) iodide solution (90ml, 0.1M, 9mmol) was added dropwise over 10mins. The solution was stirred at 0°C for 20min, quenched with aqueous sodium bicarbonate solution and then passed through silica to remove samarium salts. Chromatography on silica (hexane-ethyl acetate, 4:1 to 100% ethyl acetate) afforded pure **16** (0.12g, 29%):

Methyl (2S)-2-[(phenoxycarbonyl)[3-(4-aminophenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (16). ν_{max} ($CDCl_3$) 3470 (w), 3380 (m), 3030-2830 (s), 1720 (s), 1610 (m), 1515 (s), 1495 (m), 1470 (m), 1395 (m), 1255 (s), 1200 (s), 1180 (m), 1120 (s), 1005 (m), 970 (m) and 840 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.40-7.30 (2H, m, ArH), 7.23-7.19 (2H, d, J 8Hz, ArH), 7.20-7.05 (3H, m, ArH), 6.66-6.62 (2H, d, J 8Hz, ArH), 6.58-6.44 (1H, d, J 16Hz, CH=C<u>H</u>-Ar), 6.23-6.09 (1H, dt, J_1 16Hz, J_2 7Hz, C<u>H</u>=CH-Ar), 4.64-4.45 (2H, m, N-C<u>H</u>$_2$), 4.26-4.09 (3H, m, N-C<u>H</u> and C<u>H</u>$_2$OSi), 3.73 (3H, s, CO$_2$C<u>H</u>$_3$), 0.92 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.10 (6H, s, 2 x Si-C<u>H</u>$_3$); δ_C (200MHz, $CDCl_3$) 170.17 (<u>C</u>O$_2$CH$_3$), 154.95 (N-<u>C</u>O$_2$), 146.40, 133.35, 132.44, 129.41, 127.72, 125.50, 121.88, 121.71, 121.28, 115.18 (ArC and =<u>C</u>), 61.91, 61.51, 61.20 (N-<u>C</u>H and <u>C</u>H$_2$OSi), 52.12 (CO$_2$<u>C</u>H$_3$), 50.15 (N-<u>C</u>H$_2$), 25.70 (Si-C(<u>C</u>H$_3$)$_3$), 18.01 (Si-<u>C</u>(CH$_3$)$_3$) and -5.65 (Si-CH$_3$); m/z (DCI, NH_3) 485 ($M+H^+$, 25%), 427 (7) and 132 (100).

4-Trifluoromethylbenzaldehyde. The alcohol **18** (5.0g, 28.4mmol) was stirred in dichloromethane (25ml) at r.t.. Pyridinium chlorochromate (9.18g, 42.6mmol) was added portionwise over 5mins. The solution

rapidly turned black and the evolution of heat was such that the solvent was refluxed during addition. The solution was allowed to stir for a further 2.5h before being partitioned between water and petrol. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound[16] as an olive-green liquid (4.57g, 92%); ν_{max} (thin film) 2820-1940 (w), 1715 (s), 1390 (m), 1325 (s), 1205 (s), 1175 (s), 1130 (s), 1105 (s), 1065 (s), 1015 (m) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 10.12 (1H, s, C<u>H</u>O), 8.03 (2H, d, J 2.8Hz, ArH) and 7.81 (2H, d, J 2.8Hz, ArH); δ_C (50.3MHz, $CDCl_3$) 191.37 (<u>C</u>HO), 138.78, 136.05, 130.02 and 126.23 (ArC and =<u>C</u>); m/z (DCI, NH_3) 174 (M^+, 100%) and 145 (12).

4-Trifluoromethylcinnamaldehyde (19). 4-Trifluoromethylbenzaldehyde (4.40g, 25.3mmol) in toluene (25ml) was stirred at 80°C. (Triphenylphosphoranylidene) acetaldehyde (8.47g, 27.8mmol) was added portionwise over 5mins. The solution was stirred under argon at 80°C for 5h. The solvent was removed *in vacuo* and the residue separated on silica (petrol(30-40°C)-ethyl acetate; 9:1) to give **19** as an orange liquid (1.2g) contaminated with unhomologated material[16]; δ_H (200MHz, $CDCl_3$) 9.78, 9.66 (1H, 2 x d, J 7.5Hz, C<u>H</u>O), 7.69 (2H, s, ArH), 7.63 (2H, s, ArH), 7.56-7.48 (1H, d, J 16Hz, C<u>H</u>=CH-CHO) and 6.89-6.35 (1H, 2 x dd, J_1 16Hz, J_2 7.5Hz, CH=C<u>H</u>-CHO); δ_C (50.3MHz, $CDCl_3$) 193.77, 193.57 (<u>C</u>HO), 151.10, 150.55, 140.38, 132.97, 130.62, 128.71, 128.58, 127.72, 126.15 and 125.94 (ArC and =<u>C</u>); m/z (DCI, NH_3) 201 ($M+H^+$, 33%), 172 (10), 151 (12) and 131 (100%).

Methyl (2S)-2-[[3-(4-trifluoromethylphenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate. To a solution of **4** (2.5g) in benzene (12ml) was added 4-trifluoromethylcinnamaldehyde (2.0g, 10mmol) portionwise over 0.25h while stirring at r.t.. After 0.5h ethyl acetate was added and the solution dried ($MgSO_4$) and concentrated *in vacuo*. The crude imine was dissolved in methanol (30ml) and sodium borohydride (0.68g, 16.3mmol) added portionwise over 10mins at 0°C. After 0.2h the ice bath was removed and stirring continued for 0.5h. Water and ethyl acetate were then added and the organic layer separated,washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (petrol(30-40°C)-ethyl acetate, 19:1-4:1) afforded the title compound as a dark orange oil (1.16g, 20%); Rf 0.42 (petrol(30-40°C)-ethyl acetate, 4:1); ν_{max} (liquid film) 3400-3300 (w), 3040-2800 (s), 1740 (s), 1615 (s), 1465 (s), 1435 (m), 1415 (m), 1360 (m), 1330 (s), 1255 (s), 1130 (s), 1070 (s), 1015 (s), 990 (s), 940 (s) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.72-7.40 (4H, m, ArH), 6.93-6.80, 6.65-6.30, 6.02-5.88 (2H, m, C<u>H</u>=C<u>H</u>-Ar), 3.99-3.75 (2H, m, $C\underline{H}_2OSi$), 3.75 (3H, s, -$OC\underline{H}_3$), 3.55-3.21 (2H, m, N-$C\underline{H}_2$), 1.97 (1H, s, N<u>H</u>), 0.88 (9H, s, Si-$C(C\underline{H}_3)_3$) and 0.06, 0.05 (6H, 2 x s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 174.78 ($\underline{C}O_2CH_3$), 134.31, 133.54, 131.78, 131.07, 130.34, 127.13, 126.81, 126.56, 126.46, 126.68 (ArC and =<u>C</u>H), 109.96 (-<u>C</u>F_3), 64.49 (N-<u>C</u>H), 62.24 ($\underline{C}H_2OSi$), 51.72 (-$O\underline{C}H_3$), 49.61 (N-$\underline{C}H_2$), 25.57 (Si-$C(\underline{C}H_3)_3$), and -5.75, -5.85 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 418 ($M+H^+$, 49%), 286 (71), 202 (48), 102 (82) and 91 (100).

Methyl (2S)-2-[(phenoxycarbonyl)[3-(4-trifluoromethylphenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (20). To a solution of the previous compound (1.16g, 2.16mmol) in ethyl acetate (15ml) was added a saturated aqueous solution of sodium bicarbonate (3ml) at 0°C while stirring, followed by the addition of phenyl chloroformate (0.34g, 2.16mmol). After 1h water was added and the solution allowed to reach r.t.. The organic layer was then separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (petrol(30-40°C)-ethyl acetate, 4:1) afforded **20** as an

orange oil (1.06g, 71%); Rf 0.59 (petrol(30-40°C)-ethyl acetate, 4:1); (Found: C, 60.22; H, 6.46; N, 2.62. $C_{27}H_{34}F_3NO_5Si$ requires C, 60.32; H, 6.37; N, 2.61%); ν_{max} (liquid film) 3050-2820 (s), 1720 (s), 1615 (m), 1595 (m), 1495 (m), 1455 (s), 1415 (s), 1325 (s), 1255 (s), 1200 (s), 1175 (s), 1125 (s), 1070 (s), 1015 (m) and 905 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.70-7.10 (9H, m, ArH), 6.75-6.38 (2H, m, CH=C<u>H</u>-Ar and C<u>H</u>=CH-Ar), 4.79-4.50 (2H, m, N-C<u>H</u>$_2$), 4.39-4.11 (3H, m, N-C<u>H</u> and C<u>H</u>$_2$OSi), 3.78 (3H, s, -OC<u>H</u>$_3$), 0.97, 0.96 (9H, 2 x s, Si-C(C<u>H</u>$_3$)$_3$) and 0.15, 0.14 (6H, 2 x s, 2 x Si-C<u>H</u>$_3$); δ_C (50.3MHz, $CDCl_3$) 170.11 (<u>C</u>O$_2$CH$_3$), 156.58, 155.11, 151.35 (N-<u>C</u>O$_2$), 140.46, 132.20, 131.46, 130.85, 130.63, 129.51, 129.15, 127.08, 126.69, 125.72, 121.70, 120.04, 115.46 (ArC and <u>C</u>=), 61.89, 61.70, 61.55 (N-<u>C</u>H and <u>C</u>H$_2$OSi), 52.21 (-O<u>C</u>H$_3$), 50.28, 49.66 (N-<u>C</u>H$_2$), 25.65 (Si-C(<u>C</u>H$_3$)$_3$), 18.00 (Si-<u>C</u>(CH$_3$)$_3$) and -5.70, -5.83 (Si-<u>C</u>H$_3$); m/z (DCI, NH_3) 538 ($M+H^+$, 100%), 480 (18), 444 (8), 406 (10) and 260 (22).

Methyl (2S)-2-[(phenoxycarbonyl)-[[3-(4-trifluoromethylphenyl)prop-2-en-1-yl]amino]-3-[(*tert*-butyldimethylsilyl)oxy] propan-1-al (21). To a solution of **20** (0.47g, 0.87mmol) in dry toluene (10ml) was added diisobutylaluminium hydride (1.30ml, 1.0M, 1.30mmol) dropwise while stirring at -78°C under a nitrogen atmosphere. After 3.5h methanol (0.5ml) was added dropwise to quench the reaction followed by saturated aqueous Rochelle salt solution to stabilize the complex. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the pure aminoaldehyde **21** as a pale yellow liquid (0.37g, 83%); δ_H (200MHz, $CDCl_3$) 9.77 (1H, d, J 15.8Hz, CH-C<u>H</u>O), 7.85-7.10 (9H, m, ArH), 7.01-6.70 (1H, m, Ar-CH=C<u>H</u>), 6.70-6.39 (1H, m, Ar-C<u>H</u>=CH), 4.76-4.58 (1H, m, N-C<u>H</u>), 4.47-3.90 (4H, m, N-CH_2 and CH_2OSi), 0.98 (9H, s, Si-$(CH_3)_3$) and 0.16 (6H, 2 x s, 2 x Si-CH_3).

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-hydroxy-4-(4-trifluoromethylbenzyl) pyrrolidine (22). The aminoaldehyde **21** (0.37g, 0.73mmol) was dissolved in dry degassed tetrahydrofuran (75ml) and stirred at 0°C. To the solution was added HMPA (4ml) and *tert*-butanol (0.216g, 2.92mmol, 4 equivalents). Samarium (II) iodide solution (22ml, 0.1M, 2.2mmol) was added dropwise over 10mins. The solution was stirred at 0°C for 30min, quenched with aqueous sodium bicarbonate solution and then passed through silica to remove samarium salts. Chromatography on silica (hexane-ethyl acetate, 4:1 to 1:1) afforded pyrrolidine **22** (0.165g, 44%) as a pale yellow oil: Rf 0.40 (hexane-ethyl acetate, 3:2); ν_{max} ($CHCl_3$) 3600-3250 (w), 3040-2830 (m), 1715 (s), 1620 (w), 1495 (w), 1470 (m), 1400 (s), 1325 s), 1255 (m), 1215 (s), 1165 (s), 1125 (s), 1070 (s), 1020 (m) and 840 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.62-7.53 (2H, m, ArH), 7.48-7.38 (4H, m, ArH), 7.27-7.16 (1H, m, ArH), 7.15-7.06 (2H, m, ArH), 4.25-2.30 (10H, m, N-C<u>H</u>$_2$, N-C<u>H</u>, C<u>H</u>$_2$OSi, C<u>H</u>OH, -O<u>H</u>, C<u>H</u>CH$_2$Ar and CHC<u>H</u>$_2$Ar), 0.93 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.11, 0.10 (6H, 2 x s, 2 x Si-C<u>H</u>$_3$); δ_C (125.7MHz DEPT, $CDCl_3$) 151.84, 151.10 (N-<u>C</u>O$_2$), 143.58, 129.21, 129.07, 129.01, 125.51, 125.36, 125.27, 121.64, 121.41 (ArC and =<u>C</u>), 78.66, 77.99, 76.65, 76.38 (<u>C</u>HOH), 65.25, 65.09, 59.99, 59.79 (N-<u>C</u>H), 63.44, 62.38, 62.07, 61.69, 61.01 (<u>C</u>H$_2$OSi), 50.51, 50.10, 49.27 (<u>C</u>H$_2$Ph), 46.97, 45.81 (<u>C</u>HCH$_2$Ph), 37.11, 36.42 (N-<u>C</u>H$_2$), 25.84, 25.75 (Si-C(<u>C</u>H$_3$)$_3$), 18.13 (Si-<u>C</u>(CH$_3$)$_3$) and -5.49, -5.60 (Si-<u>C</u>H$_3$); m/z (DCI, NH_3) 510 ($M+H^+$, 100%), 492 (2), 452 (36), 416 (23), 159 (17) and 131 (34).

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