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The Synthesis Of Substituted Pyrrolidines By A Samarium (II) Iodide Mediated Ring Closure. Part 2

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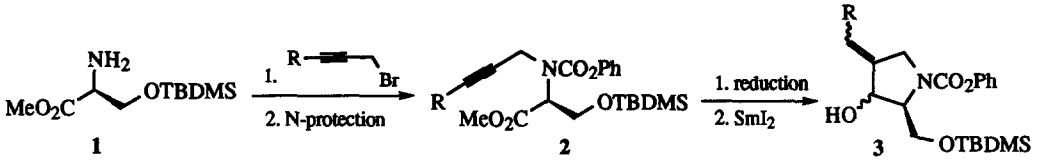
Abstract: Samarium (II) iodide-mediated ring closures, of substituted N-propargyl substrates derived from L-serine, have been used to generate a series of 2,3,4-trisubstituted pyrrolidine derivatives.

It was envisaged that the work discussed in the preceding paper could be extended from aldehyde-alkene coupling to aldehyde-alkyne coupling reactions.[1]. There exist very few examples of such samarium (II)-promoted reactions in the literature. The only systematic study was conducted by Shim and Kang[2] who examined the intramolecular couplings of a range of aldehyde and ketone groups with alkynes. They succeeded in generating 5 and 6-membered carbocyclic and heterocyclic products, in moderate to good yields, but observed higher yields and cleaner products in the formation of 5-membered, as compared to 6-membered systems.

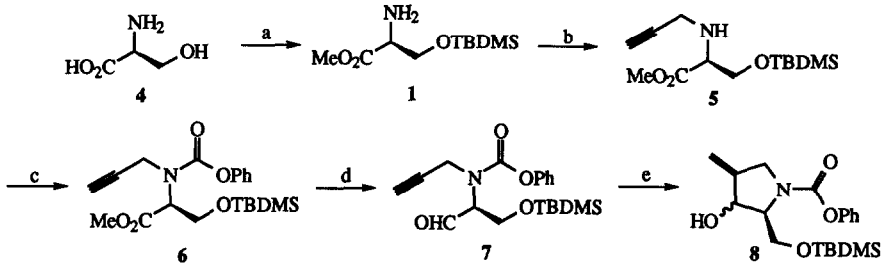


Scheme 1

It was anticipated that alkynes of the type **2**, prepared as shown from serine derivative **1**, would give higher yields of cyclised products **3** than olefins, on treatment with samarium (II) (Scheme 1). Such products would possess functionality amenable to elaboration to kainoid analogues, which are 2,3,4-trisubstituted pyrrolidines.[3]

Thus L-serine **4** was converted to the protected compound **1** (Scheme 2) as described previously.[1] This was treated with propargyl bromide in ethyl acetate, with triethylamine as a base,[4] to give the monoalkylated product **5** in 36% yield. The ^{1}H n.m.r. of the crude reaction product indicated that there were smaller quantities of the dialkylated product and some unreacted starting material. The amine was converted to aldehyde **7** by N-

protection with phenyl chloroformate, followed by reduction of the methyl ester functionality using diisobutylaluminium hydride at -78°C. Treatment of the crude aldehyde with SmI_2 at 0°C, in the presence of HMPA, gave the cyclised pyrrolidine **8** in 70% yield. This yield was considerably higher than that obtained from the related olefinic derivatives discussed in the preceding paper.[1]



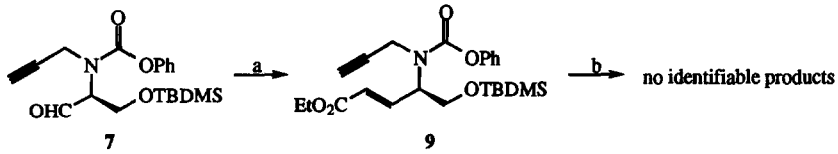
Reagents: a: HCl, MeOH then TBDMSCl, Et_3N, DMAP, $PhCH_3$, 82%. b: propargyl bromide, Et_3N, $PhCH_3$. c: PhOCOCl, $NaHCO_3$, H_2O, EtOAc, 36% over 2 steps. d: DIBAL, $PhCH_3$, -78°C, 78%. e: $2SmI_2$, ^tBuOH, HMPA, THF, 0°C.

Scheme 2

The product **8** was shown by ^1H n.m.r to be a mixture of two diastereomers in a ratio of *ca.* 6:4. These were inseparable by column chromatography or HPLC. In the ^1H n.m.r spectrum, the olefinic protons appeared as a singlet at δ 5.35 and a doublet at δ 5.20.

Molander and McKie[5] have described a procedure whereby a suitable substrate upon treatment with samarium iodide, underwent an initial reductive cyclisation and the radical generated was subsequently reduced to give an organosamarium intermediate, which was then trapped *in situ* by an appropriate aldehyde or ketone electrophile. Only small amounts (<5%) of the untrapped cyclised product were observed. Curran and Wolin[6] have reported a similar trapping experiment, where an intermolecular aldol reaction took place between the organosamarium intermediate and an added aldehyde. However, when aldehyde **7** was treated with SmI_2 in THF at -30°C, in the presence of HMPA and acetone, only the untrapped cyclised pyrrolidine **8** was obtained in 50% yield (Scheme 2).

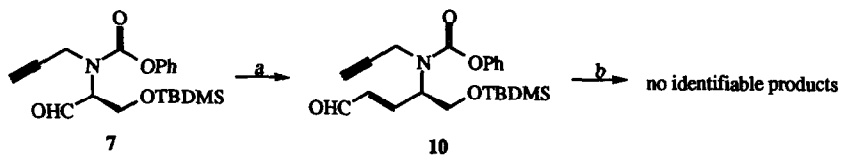
A vinylogue **9** of the aldehyde **7** was prepared as outlined in (Scheme 3). However, on reaction with samarium (II) iodide under standard conditions, no cyclised product was obtained which is consistent with the lower reactivity of vinylogous esters which has been observed previously.[7]



Reagents: a: $Ph_3P{=}CH{-}CO_2Et$, DCM, 68%. b: SmI_2, ^tBuOH, HMPA, THF, 0°C.

Scheme 3

The aminoaldehyde **7** was converted to an alternative vinylogue, the α,β-unsaturated aldehyde **10,** by Wittig homologation, with triphenylphosphoranylidene acetaldehyde in dichloromethane (Scheme 4). Treatment with with samarium (II) iodide, under standard conditions, again afforded no identifiable product.

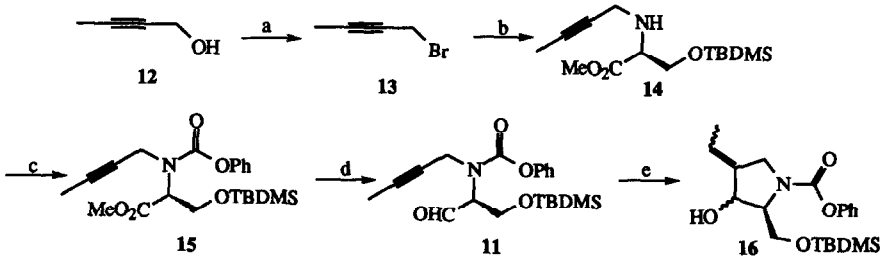


7 10

Reagents: a: Ph_3P=CH-CHO, DCM, 53%. b: SmI_2, ^tBuOH, HMPA, THF, 0°C.

Scheme 4

It was thought that a valuable insight could be provided by preparing further acetylenic analogues of **7** as precursors to pyrrolidines. It was therefore envisaged that an *N*-butynyl precursor **11** could be prepared by a similar *N*-alkylation technique to those described earlier, and subsequently cyclised with samarium (II) to give pyrrolidine **16** (Scheme 5). Thus, commercially available 2-butyn-1-ol **12** was reacted with triphenylphosphine and bromine, in dimethylformamide, to give the volatile 1-bromo-2-butyne[8] **13**. The protected L-serine derivative **1** was then alkylated with **13**, using triethylamine as the base. After reflux, a low yield of the monoalkylated product **14** was obtained, together with some dialkylated product. The amine was protected as the phenyl carbamate **15** in 73% yield.



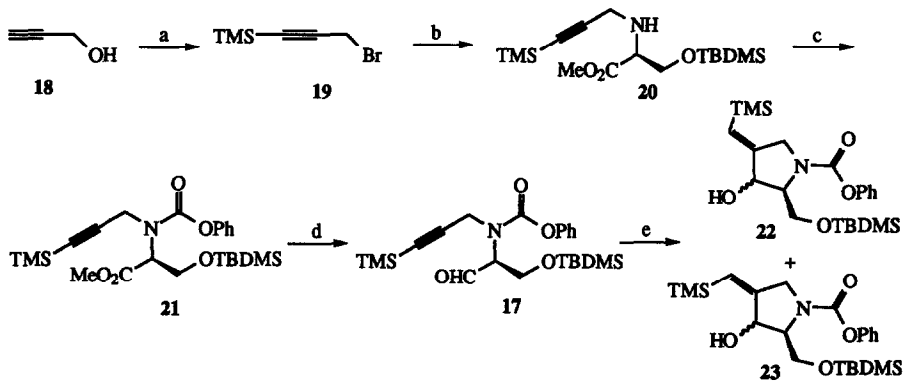
12 13 14 15 11 16

Reagents: a: PPh_3, Br_2, DMF, 35%. b: 1, Et_3N, $PhCH_3$, reflux, 19%. c: PhOCOCl, $NaHCO_3$, H_2O, EtOAc, 73%. d: DIBAL, $PhCH_3$, -78°C, 12%. e: 2SmI_2, ^tBuOH, HMPA, THF, 0°C, 50%.

Scheme 5

The methyl ester was reduced with diisobutylaluminium hydride at -78°C over 5h, giving aldehyde **12** in only 12% yield, together with unreacted ester. The crude mixture was treated with samarium (II), under standard conditions, affording pyrrolidine **16** as a colourless oil in 50% yield.

Using the same methodology described earlier, the precursor **17**, possessing a trimethylsilylpropynyl substituent, was prepared and cyclised (Scheme 6).

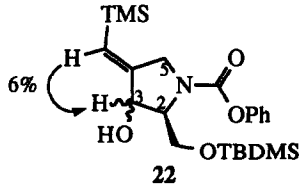


Reagents: a: 2EtMgBr, THF, Me_3SiCl then PPh_3, Br_2, DMF, 25%. b: **1**, Et_3N, $PhCH_3$, reflux, 20%. c: PhOCOCl, $NaHCO_3$, H_2O, EtOAc, 96%. d: DIBAL, $PhCH_3$, -78°C, 50%. e: $2SmI_2$, ^tBuOH, HMPA, THF, 0°C, 76%.

Scheme 6

Thus, prop-2-ynol **18** was deprotonated using 2 equivalents of ethylmagnesium bromide, and the resultant acetylenic anion quenched with trimethylsilyl chloride, to give 3-trimethylsilylprop-2-ynol[9] in 59% yield. Reaction of the alcohol with triphenylphosphine and bromine in DMF, gave the bromide[10] **19** in 43% yield (Scheme 6). The bromide was used to alkylate the protected L-serine derivative **1** by reaction in refluxing toluene, in the presence of triethylamine. This afforded the monoalkylated amine **20** in 20% yield which was converted to the *N*-protected phenyl carbamate **21**. The methyl ester **21** was converted to the aldehyde **17**, by reduction with diisobutylaluminium hydride at -78°C, in 50% yield. The aldehyde **17**, as a 1:1 mixture with unreacted **21**, was treated with samarium (II) iodide, under standard conditions, to give pyrrolidines **22** and **23** in 57% and 19% yields respectively. This was the most rapid cyclisation reaction observed, requiring only two minutes for completion. Both compounds were shown by ^1H n.m.r. spectroscopy to be mixtures of diastereomers which proved to be inseparable. A pure sample of the major isomer **22** was obtained after careful column chromatography and was shown to be a *ca.* 1:1 mixture of the 2 diastereomers. The presence of the minor isomer **23** was demonstrated by the olefinic doublet at δ 5.73, and by mass spectroscopy.

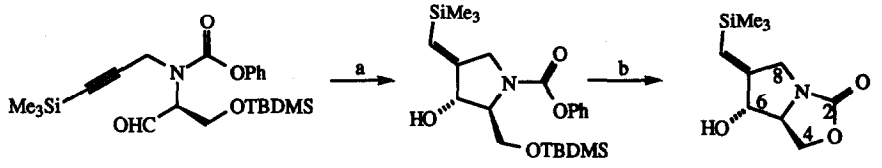
The orientation of the double bond in **22** was determined by a n.O.e. difference experiment. Irradiation of the olefinic proton at δ 5.85, gave a 6% enhancement of the H3 proton at δ 3.67, and no enhancement of the H5 protons. This strongly suggested the *E*-orientation of the double bond, as shown above.



22

In view of the high yield and rate of this cyclisation, the reaction was repeated at -70°C, with the other parameters remaining unchanged (Scheme 7). The reaction was completed in 15 minutes and gave a total yield of 65%. The *E*-:*Z*-ratio in the product was observed to have changed from *ca.* 3:1 to 7:1. A sample of the major

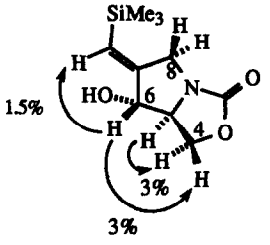
product **22a** was obtained by column chromatography and shown by ^{1}H n.m.r. spectroscopy to be a single diastereomer. The silyloxy protecting group was removed by acidic hydrolysis, in the presence of *p*-toluenesulphonic acid, to give the diol in high yield, which was then converted to oxazolidinone **24** by treatment with potassium carbonate. A n.O.e. difference experiment was performed to ascertain the stereochemistry at the C6 position of **24**. Irradiation of the H5α proton, which was of known stereochemistry through its origin from L-serine, produced a 3% enhancement of the H4α proton, but no enhancement of the H6 proton. Irradiation of the H6 proton gave a 1.5% enhancement of the vinyl proton and a 3% enhancement of the H4β proton. This strongly suggested the *R* configuration for the chiral centre at C6 and supported the *E*-geometry assigned to the double bond.



18 **22a** **24**

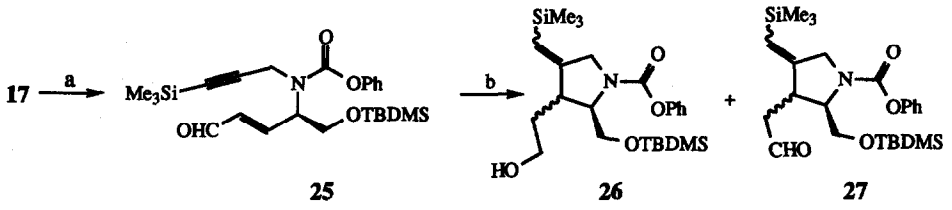
Reagents: a: $2SmI_2$, 2^tBuOH, HMPA, THF, -78°C, 56%. b: PTSA, MeOH then K_2CO_3, MeOH, H_2O, 58%.

Scheme 7



24

A vinylogue **25** of the aldehyde **17** was prepared as outlined in Scheme 8. The α,β-unsaturated aldehyde **25** was subsequently treated with 4 equivalents of SmI_2, under standard conditions, giving pyrrolidines **26** and **27** in yields of 25% and 10% respectively. The ^{1}H n.m.r. spectrum of **26** displayed a singlet at δ 5.56 and a doublet at 5.52, due to the olefinic proton in the *E*- and *Z*-isomers, which were present in a ratio of *ca.* 2.8:1. The minor product **27** was characterised on the basis of its ^{1}H n.m.r. spectrum, in which the aldehyde proton appeared as a multiplet at δ 9.7. These two products were thought to arise through the generation of an ambident radical which adds to the acetylenic trap at the β–carbon of the α,β-unsaturated aldehyde. This type of reaction has not been previously described for SmI_2. In the major product **26**, there has been subsequent reduction of the aldehyde functionality, to give a primary alcohol.



25 26 27

Reagents: a: Ph_3P=CHCHO, DCM, 32%. b: $4SmI_2$, 4^tBuOH, HMPA, THF, 0°C, 35%.

Scheme 8

In conclusion, aldehyde-alkyne couplings were observed to proceed more rapidly, and in higher yield, than the alkene-aldehyde couplings discussed in the preceding paper, although, once again, the reactions generally did not prove to be diastereoselective.

EXPERIMENTAL

Methyl (4S)-2-[(prop-2-ynyl)amino)]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (5). The amine **1** (4.0g, 17.2mmol) was dissolved in ethyl acetate (50ml) and stirred at r.t.. Propargyl bromide solution (7.0g, 80%, 47.1mmol) was added simultaneously with triethylamine (4.0g, 39.6mmol) dropwise over 0.5h and the reaction stirred for a further 20h at r.t.. The reaction mixture was refluxed (70-75°C) for 1h and allowed to cool to r.t.. Water and ethyl acetate were then added and the organic layer separated and washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded **5** as a colourless oil (1.68g, 36%); Rf 0.24 (hexane-ethyl acetate, 4:1); ν_{max} (thin film) 3300 (w), 3000-2900 (s), 1735 (s), 1460 (m), 1372 (m), 1245 (s), 1200 (s), 1105 (s), 1045 (s), 1035 (m), 835 (s) and 775 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 3.90-3.82 (2H, m, $C\underline{H}_2OSi$), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.59 (1H, t, J 4.7Hz, N-C$\underline{H}$), 3.63-3.37 (2H, m, N-$C\underline{H}_2$), 2.21 (1H, t, J 2.3Hz, C≡C$\underline{H}$), 1.47 (1H, s, N$\underline{H}$), 0.87 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.04 (6H, s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 173.2 ($\underline{C}O_2CH_3$), 81.4 ($\underline{C}$≡CH), 71.7 (C≡$\underline{C}$H), 64.3, 61.3 (N-$\underline{C}$H and $\underline{C}H_2OSi$), 51.7 ($CO_2\underline{C}H_3$), 36.5 (N-$\underline{C}H_2$), 25.5 (Si-C($\underline{C}H_3$)$_3$), 17.9 (Si-$\underline{C}$(CH_3)$_3$) and -5.7, -5.8 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 272 ($M+H^+$, 100%), 214 (18) and 182 (7).

Methyl (4S)-2-[(phenoxycarbonyl)(prop-2-ynyl)amino)]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (6). The amine **5** (0.315g, 1.16mmol) in ethyl acetate (5ml) was stirred with sodium bicarbonate solution (2ml) at 0°C, followed by the addition of phenyl chloroformate (0.15ml, 0.19g, 1.16mmol). After 2h water was added and the solution allowed to reach r.t.. The solution was then washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification on silica (hexane-ethyl acetate, 4:1) afforded **6** as a colourless oil (0.44g, 99%); Rf 0.37 (ethyl acetate:hexane, 4:1); ν_{max} (thin film) 3310-3240 (w), 3050-2830 (s), 1770-1690 (s), 1592 (m), 1445 (s), 1405 (s), 1360 (m), 1320 (m), 1250 (s), 1195 (s), 1120 (s), 990 (m), 908 (m) and 835 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.45-7.07 (5H, m, ArH), 4.90 (1H, m, J 3.5Hz, N-C$\underline{H}$), 4.63-4.32 (2H, m, N-$C\underline{H}_2$), 4.23 (2H, m, $C\underline{H}_2OSi$), 3.77 (3H, s, $CO_2C\underline{H}_3$), 2.27 (1H, t, J 2.3Hz, ≡C$\underline{H}$), 0.92 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.12, 0.10 (6H, 2 x s, 2 x Si-$C\underline{H}_3$); δ_C (50.3MHz, $CDCl_3$) 170.10 ($\underline{C}O_2CH_3$), 151.41 (N-$\underline{C}O_2$), 129.48,

125.78, 121.90, 121.74 (ArC), 80.44 (C≡CH), 71.09 (C≡CH), 62.18, 60.61 (N-CH and CH_2OSi), 52.17 (CO_2CH_3), 36.40 (N-CH_2), 25.61 (Si-C(CH_3)$_3$), 17.98 (Si-C(CH_3)$_3$) and -5.81, -6.00 (Si-CH_3); m/z (DCI, NH_3) 392 ($M+H^+$, 54%), 334 (14) and 260 (100).

(4S)-2-[(Phenoxycarbonyl)(prop-2-ynyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propanal (7). **6** (0.45g, 1.15mmol) was dissolved in dry toluene (12ml) and stirred at -78°C under nitrogen. Diisobutylaluminium hydride (1.21ml, 1.5M, 1.85mmol) was added dropwise over 0.5h and the solution then stirred for a further 2.5h. Methanol (1ml) was then added to quench the reaction followed by saturated aqueous Rochelle's salt solution to stabilize the complex. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude **7** as a pale yellow oil (0.320g); δ_H (200MHz, $CDCl_3$) 9.82, 9.71 (1H, 2 x s, -CHO), 7.50-7.05 (5H, m, ArH), 4.75-4.17 (5H, m, N-CH, N-CH_2 and CH_2OSi), 2.38 (1H, s, C≡CH), 0.92 (9H, s, Si-C(CH_3)$_3$) and 0.10 (6H, s, Si-CH_3).

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-hydroxy-4-(methylenyl)pyrrolidine (8). **7** (0.18g) was dissolved in dry, degassed tetrahydrofuran (45ml) and stirred at 0°C under an atmosphere of nitrogen. To this was added HMPA (2.25ml) and *tert*-butanol (0.122g). Samarium (II) iodide solution (17ml, 0.1M, 1.7mmol) was added dropwise over 5min and the solution stirred for a further 10min. Saturated sodium bicarbonate solution was then added to quench the reaction. The solution was filtered through silica to remove samarium salts and the filtrate concentrated *in vacuo*. Separation on silica (hexane-ethyl acetate, 4:1) afforded **8** as a pale yellow oil (0.13g, 70%): Rf 0.20 (hexane-ethyl acetate, 4:1); (Found: C, 62.63; H, 8.43; N, 3.83. $C_{19}H_{29}NO_4Si$ requires C, 62.80; H, 7.99; N, 3.86%); ν_{max} (thin film) 3600-3200 (w), 2960-2850 (m), 1735 (s), 1590 (w), 1460 (m), 1392 (s), 1205 (s), 1115 (m), 1055 (m), 985 (m), 835 (s), 780 (s) and 750 (s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 7.42-7.11 (5H, m, ArH), 5.35 (1H, s, =CH), 5.21-5.19 (1H, d, J 9.8Hz, =CH), 4.64 (1H, s, CH-OH), 4.49, 4.17 (1H, 2 x d, J 15Hz, N-CH_2), 4.42, 4.04 (1H, 2 x d, J 15Hz, N-CH_2), 4.10 (0.5H, m, N-CH in 1 diastereomer), 3.97-3.93 (2.5H, m, CH_2OSi and N-CH in 1 diastereomer), 3.71-3.62 (1H, m, CH-OH), 0.89 (9H, s, Si-C(CH_3)$_3$) and 0.06 (6H, s, Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 129.47, 125.50, 121.92, 121.83, 110.44 (ArC), 67.05, 66.95 (N-CH), 61.86 (CH_2OSi), 50.30, 50.05 (CH-OH), 36.70 (N-CH_2), 25.71 (Si-C(CH_3)$_3$) and -5.07 (Si-CH_3); m/z (DCI, NH_3) 364 ($M+H^+$, 12%), 306 (10), 270 (5), 202 (8), 108 (22) and 94 (100).

Ethyl (4R)-4-[(phenyloxycarbonyl)(prop-2-ynyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-enoate (9). **7** (0.35g, 0.97mmol) was dissolved in dichloromethane (12ml) and ethyl (triphenylphosphoranylidene) acetate (0.74g, 2.1mmol) 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 the α,β-unsaturated ester **9** as a colourless liquid (0.29g, 68%); Rf 0.40 (hexane-ethyl acetate, 4:1); ν_{max} (thin film) 3440 (w), 3310 (m), 3070-2850 (s), 2123 (w), 1750-1690 (s), 1660 (m), 1595 (m), 1495 (s), 1445 (s), 1405 (s), 1365 (s), 1255 (s), 1120 (s), 1045 (s), 1005 (s), 940 (s), 911 (m) and 839 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.49-7.03 (5H, m, ArH), 6.95-6.75 (1H, m, CH=CH-CO_2), 6.19-6.02 (1H, m, =CH-CO_2), 4.81 (1H, m, N-CH), 4.43-3.93 (6H, m, N-CH_2, -$CO_2CH_2CH_3$ and CH_2OSi), 2.30(1H, m, C≡CH), 1.31 (3H, m, $CO_2CH_2CH_3$), 0.92 (9H, s, Si-C(CH_3)$_3$) and 0.10 (6H, s, Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 166.42 (CO_2CH_2), 151.56 (N-CO_2), 143.81, 129.82, 125.88, 123.89, 122.02 (ArC and =C), 71.90 (C≡CH), 62.87 (N-

CH), 60.88 (CH_2OSi), 35.81 (N-CH_2), 25.61 (Si-C(CH_3)$_3$), 17.93 (Si-C(CH_3)$_3$) and -5.77 (Si-CH_3); m/z (DCI, NH_3) 432 ($M+H^+$, 100%), 374 (30), 300 (39), 257 (23) and 180 (27).

(4S)-4-[(Phenyloxycarbonyl)(prop-2-ynyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-en-1-al (10). To a solution of **7** (0.36g, 0.10mmol) in dichloromethane was added (triphenylphosphoranylidene) acetaldehyde (0.49g, 1.617mmol) portionwise over 15min. The solution was stirred for 20h under a nitrogen atmosphere. The solvent was then removed *in vacuo* to give a dark red oil. Separation on silica (petrol(60-80°C)-ethyl acetate, 4:1) afforded the αβ-unsaturated aldehyde **10** as an orange oil (0.20g, 53%); Rf 0.21 (petrol(60-80°C)-ethyl acetate, 4:1); ν_{max} (thin film) 3420-3290 (m), 3045-2850 (s), 2037 (w), 1760-1670 (s), 1645 (m), 1605 (s), 1595 (s), 1480 (s), 1360 (s), 1255 (s), 1165 (s), 1115 (s), 1025 (s), 1005 (s), 940 (s) and 911 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 9.60 (1H, d, J 9Hz, =CH-CHO), 7.50-7.09 (5H, m, ArH), 6.33 (1H, m, CH=CH-CHO), 5.74 (1H, m, CH=CH-CHO), 4.62 (1H, m, N-CH), 3.85 (2H, m, CH_2-C≡), 3.80 (2H, m, CH_2OSi), 2.22 (1H, m, C≡CH), 0.96 (9H, s, Si-C(CH_3)$_3$) and 0.12 (6H, s, Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 193.81 (=CH-CHO), 154.64, 151.18 (CO_2), 133.01, 129.82, 125.87, 121.90, 120.13, 115.83 (ArC and =C), 71.91 (C≡CH), 62.37 (N-CH and CH_2OSi), 44.02 (N-CH_2), 25.69 (Si-C(CH_3)$_3$), 18.10 (Si-C(CH_3)$_3$) and -5.78 (Si-CH_3); m/z (DCI, NH_3) 388 ($M+H^+$, 100%), 330 (40), 294 (28), 155 (25), 193 (24) and 162 (37).

1-Bromo-2-butyne(13).[8] 2-Butyn-1-ol **12** (5.0g, 70.1 mmol) in dimethylformamide (40ml) was added with stirring to a cooled, freshly prepared solution of triphenylphosphine (45.6g, 0.174mmol) and bromine (6.3ml) in dimethylformamide (180ml). The solution was allowed to reach r.t. over 18h before extracting the mixture with petrol (60-80°C) (2 x 80ml). The organic extract was dried ($MgSO_4$) and the solvent removed carefully *in vacuo*. Distillation of the residue yielded a colourless mobile liquid which proved to be an inseparable mixture of **13** and dimethylformamide; δ_H (200MHz, $CDCl_3$) 3.89 (2H, m, C≡C-CH_2Br) and 1.84 (3H, s, C≡C-CH_3).

Methyl (4S)-2-[(but-2-ynyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (14). The amine **1** (2.0g, 8.44mmol) was dissolved in ethyl acetate (20ml) and stirred at r.t.. The bromide in dimethylformamide (4.5g) was added simultaneously with triethylamine (1.40g, mmol) dropwise over 0.5h. The reaction mixture was heated (70-75°C) for 3h and stirred for a further 20h at r.t.. Water and ethyl acetate were then added and the organic layer separated and washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (petrol(30-40°C)-ethyl acetate, 4:1) afforded **14** as a colourless oil (0.47g, 19%); Rf 0.28 (hexane:ethyl acetate, 4:1); ν_{max} (thin film) 3670-3600 (w), 3980-2840 (s), 2360 (m), 2250 (s), 1740 (s), 1465 (m), 1360 (m), 1260 (s) and 1110 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 3.92-3.75 (2H, m, CH_2OSi), 3.72 (3H, s, CO_2CH_3), 3.55 (1H, t, J 4.6Hz, N-CH), 3.49-3.33 (2H, m, N-CH_2), 1.99 (1H, s, NH), 1.79 (1H, t, J 2.3Hz, C≡CH), 0.90 (9H, s, Si-C(CH_3)$_3$) and 0.08 (6H, s, 2 x Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 173.47 (CO_2CH_3), 81.05 (C≡C-CH_3), 79.24 (C≡C-CH_3), 64.35, 61.51 (N-CH and CH_2OSi), 51.69 (CO_2CH_3), 36.98 (N-CH_2), 25.48 (Si-C(CH_3)$_3$), 17.98, 17.81 (Si-C(CH_3)$_3$), 3.30 (C≡C-CH_3) and -5.77 (Si-CH_3); m/z (DCI, NH_3) 286 ($M+H^+$, 100%) and 228 (4).

Methyl (2S)-[(phenoxycarbonyl)(but-2-ynyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (15). The amine **14** (0.43g, 1.51mmol) in ethyl acetate (10ml) was stirred with sodium bicarbonate solution

(2ml) at 0°C, followed by the addition of phenyl chloroformate (0.24ml, 1.51mmol). After 2h water was added and the solution allowed to reach r.t.. The solution was then washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification on silica (hexane-ethyl acetate, 4:1) afforded **15** as a colourless oil (0.45g, 73%); Rf 0.39 (hexane-ethyl acetate, 4:1); ν_{max} (thin film) 2980-2800 (s), 2255 (w), 1760-1710 (s), 1595 (w), 1490 (s), 1440 (s), 1410 (m), 1385 (m), 1350 (m), 1255 (s), 1205 (s), 1165 (m), 1120 (s) and 1026 (m) cm^{-1}; δ_H (200MHz,$CDCl_3$) 7.45-7.05 (5H, m, ArH), 4.90-4.80 (1H, m, N-C<u>H</u>), 4.57-3.89 (4H, m, N-C<u>H</u>$_2$ and C<u>H</u>$_2$OSi), 3.80 (3H, s, $CO_2C\underline{H}_3$), 1.84 (3H, s, ≡C-C<u>H</u>$_3$), 0.92 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.10 (6H, s, Si-C<u>H</u>$_3$); δ_C (50.3MHz, $CDCl_3$) 170.93 ($\underline{C}O_2CH_3$), 151.21 (N-$\underline{C}O_2$), 129.43, 125.60, 121.88, 121.70 (Ar<u>C</u>), 80.12 (<u>C</u>≡C), 63.47, 61.84, 60.58 (N-<u>C</u>H and <u>C</u>H$_2$OSi), 52.45, 52.08 ($CO_2\underline{C}H_3$), 36.90 (N-<u>C</u>H$_2$), 25.55 (Si-C(<u>C</u>H$_3$)$_3$), 18.02 (Si-<u>C</u>(CH$_3$)$_3$), 3.43 (C-<u>C</u>H$_3$) and -5.87 (Si-<u>C</u>H$_3$); m/z (DCI, NH_3) 406 ($M+H^+$, 100%), 390 (4), 348 (53), 312 (38) and 274 (37).

(4S)-2-[(Phenoxycarbonyl)(but-2-ynyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propanal (11). To a solution of **15** (0.41g, 1.09mmol) in dry toluene (15ml) was added diisobutylaluminium hydride (1.06ml, 1.5M, 1.59mmol) 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 **11** as a pale yellow liquid (0.36g, 12% aldehyde by ^1H nmr); δ_H (200MHz, $CDCl_3$) 9.82 (1H, s, C<u>H</u>O), 7.45-7.08 (5H, m, ArH), 4.87 (1H, t, N-C<u>H</u>), 4.55-3.75 (4H, m, N-C<u>H</u>$_2$ and C<u>H</u>$_2$OSi), 1.84 (3H, s, ≡C-C<u>H</u>$_3$), 0.92 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.11 (6H, s, Si-C<u>H</u>$_3$);

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-hydroxy-4-(ethylidene)pyrrolidine (16). The crude aminoaldehyde **11** (0.047g, 0.125mmol) was dissolved in dry degassed tetrahydrofuran (50ml) and stirred at 0°C. To the solution was added DMPU (3ml) and *tert*-butanol (0.04g, 4 equivalents). Samarium (II) iodide solution (5ml, 0.1M, 0.5mmol) was added dropwise over 1min. The solution was stirred at 0°C for 15min, 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 **16** as a colourless oil (0.025g, 50%); δ_H (200MHz, $CDCl_3$) 7.39-7.12 (5H, m, ArH), 5.66 (1H, m, =C<u>H</u>-CH$_3$), 4.25-3.48 (7H, m, N-C<u>H</u>$_2$, C<u>H</u>OH, CHO<u>H</u>, C<u>H</u>$_2$OSi and N-C<u>H</u>), 1.83 (3H, m, =CH-C<u>H</u>$_3$), 0.93 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.12 (6H, s, Si-C<u>H</u>$_3$); m/z (DCI, NH_3) 378 ($M+H^+$, 28%), 320 (9), 284 (11), 249 (32) and 232 (100); accurate mass spectrum m=320, calculated 320.1318, found 320.1317.

Evidence for a second double bond isomer was provided by the presence of signals in the ^1H nmr spectrum at δ 5.78 (1H, m, C=C<u>H</u>) and δ 1.70 (3H, m, =CH-C<u>H</u>$_3$) in approximate ratio 6:1 with the major isomer.

3-Trimethylsilylprop-2-ynol.[9] Prop-2-ynol **18** (7.0g, 0.125mol) was added with cooling, to a solution of ethyl magnesium bromide [from magnesium (6.1g) and ethyl bromide (27.5g)] in tetrahydrofuran (50ml) over 1.5h. The mixture was stirred at r.t. for 0.75h and then treated with trimethylsilyl chloride (28.0g, 0.258mol) added over 1.5h. After stirring for 18h saturated ammonium chloride solution was added and the stirring continued until all the solid had dissolved. The organic layer was then separated and the aqueous phase washed with ether (2 x 60ml). The combined organic extracts were concentrated *in vacuo*, dissolved in

anhydrous ethanol (50ml) and stirred with ice (12g) and concentrated hydrochloric acid (0.25ml) for 2h. The mixture was diluted with water (50ml) and extracted with ether (2 x 150ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled under reduced pressure to yield the title compound as a clear mobile liquid (9.38g, 59%) (b.p. 95°C, 16mmHg; lit.[9] 61°C, 2mmHg); δ_H (200MHz, $CDCl_3$) 4.26 (2H, s, C≡C-CH_2), 2.22 (1H, s, -O<u>H</u>) and 0.17 (9H, s, 3 x Si-CH_3).

3-Bromo-1-trimethylsilylprop-1-yne (19).[10] The previous compound (9.38g, 73.3mmol) in dimethylformamide (40ml) was added with stirring to a cooled, freshly prepared solution of triphenylphosphine (46.9g, 0.179m) and bromine (6.5ml) in dimethylformamide (190ml). The solution was allowed to reach r.t. over 18h before extracting the mixture with petrol (60-80°C) (2 x 80ml). The organic extract was dried ($MgSO_4$) and the solvent removed carefully *in vacuo*. Distillation of the residue yielded **19** as a colourless mobile liquid (b.p. 94-96°C, 16mmHg; lit.[10] 71-73°C, 26mmHg) (6.04g, 43%); ν_{max} (thin film) 2965 (s), 2900 (w), 2180 (m), 1680 (w), 1420 (w), 1250 (s), 1205 (s), 1040 (s), 845 (s), 760 (s) and 700 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 3.92 (2H, s, C≡C-CH_2Br) and 0.19 (9H, s, 3 x Si-CH_3); m/z (DCI, NH_3) 194, 192 ($M+H^+$, 19%), 110 (17) and 74 (100).

Methyl (4S)-2-[(3-trimethylsilylprop-2-ynyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (20) The amine **1** (2.0g, 8.44mmol) was placed in a flask with toluene (25ml) and stirred at r.t.. **19** (1.72g, 9.0mmol) and triethylamine (1.32g, 12.9mmol) were added simultaneously over 0.5h with stirring. The solution was refluxed at 70°C for 2h and then allowed to cool over 3h. Water and ethyl acetate were added and the organic layer separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (petrol(60-80°C)-ethyl acetate, 4:1) afforded **20** (0.60g, 20%); Rf 0.54 (petrol(60-80°C)-ethyl acetate, 4:1); ν_{max} (thin film) 3100-2860 (w), 1710 (s), 1660 (w), 1500 (w), 1450 (w), 1410 (s), 1355 (m), 1300 (m), 1265 (m), 1180 (m), 1115 (m), 1045 (m) and 980 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 3.80 (2H, m, CH_2OSi), 3.71 (3H, s, CO_2CH_3), 3.62-3.47 (3H, m, N-C<u>H</u> and N-CH_2), 2.12 (1H, s, N<u>H</u>), 0.85 (9H, s, Si-C(CH_3)$_3$), 0.13 (9H, s, 3 x Si-CH_3) and 0.07, 0.08 (6H, 2 x s, 2 x Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 173.22 (CO_2CH_3), 103.52 (C≡C-Si), 88.26 (C≡C-Si), 64.30, 61.45 (N-CH and CH_2OSi), 51.72 (CO_2CH_3), 37.66 (N-CH_2), 25.56, 25.48 (Si-C(CH_3)$_3$), 17.97, 17.80 (Si-C(CH_3)$_3$), -0.32, -0.38 (Si-CH_3) and -5.73, -5.86 (Si-CH_3); m/z (DCI, NH_3) 344 ($M+H^+$, 100%), 286 (18) and 73 (33).

Methyl (4S)-2-[(phenoxycarbonyl)(3-trimethylsilylprop-2-ynyl)amino)]-3-[(*tert*-butyldimethylsilyl)oxy] propionate (21). The amine **20** (0.786g, 2.29mmol) in ethyl acetate (8ml) was stirred with sodium bicarbonate solution (3ml) at 0°C, followed by the addition of phenyl chloroformate (0.29ml, 0.37g, 2.29mmol). After 2h water was added and the solution allowed to reach r.t.. The solution was then washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification on silica (hexane-ethyl acetate, 9:1) afforded **21** as a colourless oil (1.02g, 96%); Rf 0.37 (hexane-ethyl acetate, 4:1); (Found: C, 59.65; H, 8.10; N, 2.84; $C_{23}H_{37}NO_5Si_2$ requires C, 59.61; H, 7.99; N, 3.02%); ν_{max} (thin film) 2980-2810 (s), 2180 (w), 1765-1705 (s), 1595 (w), 1495 (m), 1445 (s), 1405 (s), 1360 (m), 1325 (m), 1250 (s), 1195 (s), 1120 (s), 1010 (s) 940 (w), 915 (w) and 845 (s) cm^{-1}; δ_H (200MHz,$CDCl_3$) 7.42-7.07 (5H, m, ArH), 4.89 (1H, t, J 9.7Hz, N-C<u>H</u>), 4.52-4.40 (2H, m, N-CH_2), 4.23 (2H, m, CH_2OSi), 3.76 (3H, s, CO_2CH_3), 0.92 (9H, s, Si-C(CH_3)$_3$), 0.18 (9H, s, 3 x Si-CH_3) and 0.11 (6H, s, 2 x Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 170.11 (CO_2-CH_3), 129.39,

125.65, 121.86 (ArC), 102.34 (C≡C-Si), 89.58 (C≡C-Si), 62.17, 60.43 (N-CH and CH_2OSi), 52.05 (CO_2CH_3), 37.24 (N-CH_2), 25.59 (Si-C(CH_3)$_3$), 17.96 (Si-C(CH_3)$_3$), -0.35 (Si-CH_3) and -5.82 (Si-CH_3); m/z (DCI, NH_3) 464 ($M+H^+$, 100%), 406 (71), 370 (48) and 332 (21).

Methyl (4S)-2-[(phenoxycarbonyl)(3-trimethylsilylprop-2-ynyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy] propanal (17). The methyl ester **21** (0.702g, 1.5mmol) was dissolved in dry toluene (15ml) and stirred at -78°C under nitrogen. Diisobutylaluminium hydride (1.48ml, 1.5M, 2.2mmol) was added dropwise over 0.5h and the solution then stirred for a further 5h. Methanol (1ml) was then added to quench the reaction followed by saturated aqueous Rochelle's salt solution to stabilize the complex. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **17** and unreacted **21** (1:1) as a pale yellow oil (0.68g) which was used without further purification; δ_H (200MHz,$CDCl_3$) 9.83, 9.72 (1H, 2 x s, -CHO), 7.47-7.05 (5H, m, aromatics), 4.75-3.92 (5H, m, N-CH, N-CH_2 and CH_2OSi), 0.92 (9H, s, Si-C(CH_3)$_3$), 0.18 (9H, s, 3 x Si-CH_3) and 0.10 (6H, s, Si-CH_3).

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-hydroxy-4-trimethylsilylmethylene pyrrolidine (22 and 23). The crude aldehyde **17** (0.65g, 50% aldehyde) was dissolved in dry, degassed tetrahydrofuran (80ml) and stirred at 0°C under an atmosphere of nitrogen. To this was added HMPA (4ml) and *tert*-butanol (0.167g, 3 equivalents). Samarium (II) iodide solution (33ml, 0.1M, 3.3mmol) was added dropwise over 2min and the solution stirred for a further 5min. Saturated sodium bicarbonate solution was then added to quench the reaction. The solution was filtered through silica to remove samarium salts and the filtrate concentrated *in vacuo*. Separation on silica (hexane-ethyl acetate, 9:1-2:1) afforded pyrrolidines **22** and **23** as a pale colourless oil (0.25g, 76%) which was shown to be an inseparable mixture of the two double bond isomers in ratio 3:1.

22; Rf 0.47 (hexane-ethyl acetate, 1:1); (Found: C, 60.51; H, 9.13; N, 3.15. $C_{22}H_{37}NO_4Si_2$ requires C, 60.64; H, 8.56; N, 3.21%); ν_{max} ($CHCl_3$) 3500-3300 (w), 3020-2855 (m), 1714 (s), 1495 (w), 1470 (w), 1405 (s), 1250 (m), 1215 (s), 1165 (s), 1115 (s), 1050 (w), 840 (s) and 765 (s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 7.37-7.14 (5H, m, ArH), 5.85 (1H, s, =CH), 4.51-4.16 (1H, 2 x d, J 16Hz, N-CH_2), 4.43-4.05 (1H, 2 x d, J 16Hz, N-CH_2), 4.52 (1H, s, -OH), 4.05-3.93 (1H, m, N-CH), 3.90 (2H, d, J 7Hz, CH_2OSi), 3.78-3.67 (1H, 2 x dd, J_1 10Hz, J_2 7Hz, CH-OH), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.16 (9H, s, 3 x Si-CH_3) and 0.07 (6H, s, 2 x Si-CH_3). n.O.e. experiment: irradiation at δ5.85 (=CH) gave an enhancement of 6% at δ3.78-3.67 (CH-OH); δ_C (50.3MHz, $CDCl_3$) 153.27, 151.30 (N-CO_2), 129.40, 126.26, 125.45, 121.96 (ArC), 78.56, 65.82 (N-CH), 62.17 (CH_2OSi), 49.80, 49.54 (N-CH_2), 25.74 (Si-C(CH_3)$_3$), 17.97 (Si-C(CH_3)$_3$), -0.94 (Si-CH_3) and -5.70 (Si-CH_3); m/z (DCI, NH_3) 436 ($M+H^+$, 100%), 420 (16), 378 (88), 342 (64) and 73 (50).

(5S, 6S)-1-Aza-6-hydroxy-3-oxa-2-oxo-7-trimethylsilylmethylenylbicyclo-[3.3.0^{1,5}]-octane (24). The vinyl silane **22a** (0.256g, 0.589mmol) was dissolved in methanol (9ml) and stirred at r.t.. *p*-Toluenesulphonic acid monohydrate (0.216g, 1.14mmol) was added and the reaction mixture stirred for 0.5h. Sodium bicarbonate solution was then added to quench the reaction and the aqueous mixture extracted with ethyl acetate. The extracts were washed with water, brine, dried ($MgSO_4$) and then concentrated *in vacuo* to give crude diol as a yellow oil (0.17g, 90%); δ_H (200MHz, $CDCl_3$) 7.45-7.07 (5H, m, ArH), 5.86 (1H, s,

C=CH), 4.60-3.35 (7H, m, N-CH_2, CH_2OH, N-CH, CHOH and OH), 0.89 (1H, br s, -OH) and 0.18, 0.14 (9H, 2 x s, 3 x Si-CH_3).

The diol (0.17g, 0.53mmol) was stirred with potassium carbonate (0.11g) in methanol : water (10:1, 11ml) for 2h. The reaction mixture was concentrated *in vacuo* and ethyl acetate added. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was separated on silica (hexane:ethyl acetate, 3:2) to give a colourless oil which was crystallised from ethyl acetate-hexane by vapour diffusion to give colourless crystals of **24** (0.070g, 58%); Rf 0.09 (hexane-ethyl acetate, 3:2): major double bond isomer (*E*); $[\alpha]_D^{22}$ +116.7° (c 0.37, $CHCl_3$); ν_{max} ($CHCl_3$) 3600-3200 (m), 3000-2840 (m), 1760-1720 (s), 1645 (w), 1480 (w), 1460 (w), 1405 (s), 1335 (m), 1250 (s), 1205 (s), 1130 (m), 1090 (m), 1010 (m), 980 (w) and 910 (s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 5.80 (1H, m, C=CH), 4.58-4.54 (1H, dd, J 9.3Hz, 7.8Hz, CH_2O (H4α)), 4.48-4.44 (1H, dd, J_1 9.3Hz, J_2 2.8Hz, CH_2O (H4β)), 4.28-4.24 (1H, m, N-CH_2 (H8α)), 4.22-4.20 (1H, m, CHOH (H6β)), 3.94-3.90 (1H, m, N-CH_2 (H8β)), 3.67 (1H, m, J_1 7.8Hz, J_2 2.8Hz, N-CH (H5α)), 2.28 (1H, br s, -OH) and 0.14 (9H, s, 3 x Si-CH_3); δ_H (500MHz COSY, $CDCl_3$) 5.80 (=CH) crosspeak with 4.28-4.24 (H8α), 4.22-4.20 (H6β) and 3.94-3.90 (H8β); 4.58-4.54 (H4α) crosspeak with 4.48-4.44 (H4β) and 3.67 (H5α); 4.48-4.44 (H4β) crosspeak with 4.58-4.54 (H4α) and 3.67 (H5α); 4.28-4.24 (H8α) crosspeak with 5.80 (=CH) and 3.94-3.90 (H8β); 4.22-4.20 (H6β) crosspeak with 5.80 (=CH) and 3.67 (H5α); 3.94-3.90 (H8β) crosspeak with 5.80 (=CH) and 4.28-4.24 (H8α); 3.67 (H5α) crosspeak with 4.58-4.54 (H4α), 4.48-4.44 (H4β) and 4.22-4.20 (H6β); n.O.e. experiment (500MHz, $CDCl_3$) irradiation at δ4.60 (4α) gave enhancements of 14% at δ4.48-4.44 (H4β) and 8% at δ3.67 (H5α). Irradiation at δ4.45 (4β) gave enhancements of 8% at δ4.58-4.54 (H4α), 4% at δ4.22-4.20 (H6β) and 2% at δ3.67 (H5α). Irradiation at δ4.30 (8α) gave enhancement of 14% at δ3.94-3.90 (H8β). Irradiation at δ4.25 (6β) gave enhancements of 1.5% at δ5.80 (=CH) and 3% at δ4.48-4.44 (H4β). Irradiation at δ3.95 (8β) gave enhancement of 15.4% at δ4.28-4.24 (H8α). Irradiation at δ3.70 (5α) gave enhancement of 3% at δ4.58-4.54 (H4α); δ_C (125.7MHz, $CDCl_3$) 161.10 (N-CO_2), 155.12 (C=CH-$SiMe_3$), 122.91 (=CH-$SiMe_3$), 76.59 (CHOH), 66.62 (CH_2O), 63.68 (N-CH), 49.01 (N-CH_2) and -0.75 (Si-CH_3); m/z (DCI, NH_3) 228 ($M+H^+$, 100%), 212 (27), 168 (6) and 154 (6). Minor double bond isomer (*Z*): δ_H (500MHz, $CDCl_3$) 5.69 (1H, q, J 2.2Hz, =CH), 4.58-4.53 (1H, m, CH_2O), 4.44-4.43 (1H, m, CH_2O), 4.28-4.21 (2H, dd, N-CH_2), 3.91-3.88 (1H, dt, J 2Hz, CHOH), 3.84 (1H, dt, J_1 7.5Hz, J_2 2.9Hz, N-CH) and 0.14 (9H, s, 3 x Si-CH_3); δ_C (125.7MHz, $CDCl_3$) 161.10 (N-CO_2), 155.12 (C=CH-$SiMe_3$), 126.62 (=CH-$SiMe_3$), 76.16 (CHOH), 67.00 (CH_2O), 65.95 (N-CH), 52.05 (N-CH_2) and -0.04 (Si-CH_3).

(4S)-4-[(Phenyloxycarbonyl)(3-trimethylsilylprop-2-ynyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-en-1-al (25). To a solution of the aldehyde **17** (0.80g, 1.85mmol) in dichloromethane (40ml) was added (triphenylphosphoranylidene) acetaldehyde (0.492g, 1.6mmol) portionwise over 15min. The solution was stirred for 18h under a nitrogen atmosphere. The solvent was then removed *in vacuo* to give a dark red oil. Separation on silica (petrol(60-80°C)-ethyl acetate, 19:1-4:1) afforded the α,β-unsaturated aldehyde **25** as an orange oil (0.270g, 32%); Rf 0.17 (petrol(60-80°C)-ethyl acetate, 9:1); ν_{max} (thin film) 2980-2840 (m), 2255 (w), 1720 (s), 1680 (s), 1470 (w), 1440 (w), 1405 (w), 1255 (s), 1205 (s), 1105 (m) and 1005 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 9.61 (1H, d, J 7.6Hz, =CH-CHO), 7.45-7.00 (5H, m, ArH), 6.97-6.78 (1H, dd, J_1 16Hz, J_2 7.6Hz, CH=CH-CHO), 6.42-6.28 (1H, dd, J_1 16Hz, J_2 7.6Hz, CH=CH-CHO), 4.89-4.77 (1H, m, N-CH), 4.50-4.00 (4H, m, N-CH_2 and CH_2OSi), 0.93 (9H, s, Si-$C(CH_3)_3$), 0.19 (9H, s, 3 x Si-CH_3) and 0.12 (6H, s, 2 x Si-CH_3); δ_C (50.3MHz, $CDCl_3$) 193.67 (=CH-CHO), 152.56 (NCO_2), 133.82 (CH=CH-CHO), 129.51, 125.86,

121.83 (C=), 97.37 (CH=CH-CHO), 97.37 (C≡C-Si(CH_3)$_3$), 62.65, 60.06 (N-CH and CH_2OSi), 37.42, 37.25 (N-CH_2), 25.64 (Si-C(CH_3)$_3$), -0.46 (Si-CH_3) and -5.67 (Si-CH_3); m/z (DCI, NH_3) 460 ($M+H^+$, 100%), 402 (36), 366 (15), 213 (42) and 155 (19).

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-(2-hydroxyethyl)-4-(trimethylsilylmethylenyl)pyrrolidine (26).

(2R)-*N*-(Phenyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]-3-(ethan-2-al)-4-(trimethylsilylmethylenyl)pyrrolidine. (27). The αβ-unsaturated aldehyde **25** (0.24g, 0.52mmol) was dissolved in dry, degassed tetrahydrofuran (60ml) and stirred at 0°C under an atmosphere of nitrogen. To this was added HMPA (3ml) and *tert*-butanol (0.155g, 4 equivalents). Samarium (II) iodide solution (16ml, 0.1M, 1.6mmol) was added dropwise over 0.5min and the solution stirred for a further 15min. Saturated sodium bicarbonate solution was then added to quench the reaction. The solution was filtered through silica to remove samarium salts and the filtrate concentrated *in vacuo*. Separation on silica (dichloromethane-ethyl acetate, 9:1-3:2) afforded alcohol **26** (0.060g, 25%) and aldehyde **27** (0.025g, 10%), both as colourless oils:

26: Rf 0.33 (dichloromethane-ethyl acetate, 1:1); ν_{max} (liquid film) 3550-3350 (w), 3040-2840 (m), 1715 (s), 1640 (w), 1595 (w), 1495 (m), 1470 (m), 1400 (m), 1400 (s), 1250 (s), 1165 (m) and 1060 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 7.39-7.35 (2H, m, ArH), 7.22-7.19 (1H, m, ArH), 7.16-7.13 (2H, m, ArH), 5.56 (1H, 2 x s, =CH), 4.36-4.01 (2H, m, N-CH_2), 4.01-3.90 (1H, m, N-CH), 3.86-3.75 (3H, m, CH_2OSi and CHOH), 3.59-3.54 (1H, m, CHCH$_2$CH$_2$OH), 2.89 (2H, t, J 6Hz, CH_2OH), 1.78 (2H, m, CH_2CH$_2$OH), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.18 (9H, s, 3 x Si-CH_3) and 0.13, 0.07 (6H, 2 x s, 2 x Si-CH_3); δ_C (125.7MHz, $CDCl_3$) 156.85, 155.69 (N-CO_2), 153.06, 151.29, 129.22, 125.22, 123.03, 122.25 (ArC and =C), 64.22, 63.39, 63.28 (N-CH and CH_2OH), 60.73 (CH_2OSi), 50.38, 50.11 (N-CH_2), 47.38, 46.32 (CHCH$_2$CH$_2$), 38.16 (CHCH$_2$CH$_2$), 25.89 (Si-C(CH_3)$_3$), 19.01 (Si-C(CH_3)$_3$), -0.04, -0.56 (Si-CH_3) and -5.44 (Si-CH_3); m/z (DCI, NH_3) 464 ($M+H^+$, 100%), 448 (5), 406 (61) and 370 (41).

27: Rf 0.45 (dichloromethane-ethyl acetate, 1:1); δ_H (200MHz, $CDCl_3$) 9.87-9.66 (1H, m, CH_2-CHO), 7.44-7.07 (5H, m, ArH), 6.24-6.20 (1H, s, =CH in 1 isomer), 5.88 (1H, s, =CH in 1 isomer), 4.5-1.5 (ring protons and CH_2O-), 0.92 (9H, s, Si-C(CH_3)$_3$), 0.19 (9H, s, 3 x Si-CH_3) and 0.14, 0.08 (6H, 2 x s, 2 x Si-CH_3).

REFERENCES

1. Baldwin, J.E.; MacKenzie Turner, S.C.; Moloney, M.G.,*Tetrahedron Lett.*, 1992, **33**, 1517 and preceding paper.
2. Shim, S.C.; Hwang, J.T.; Kang, H.Y.; Chang, M.H., *Tetrahedron Lett.*, 1990, **33**, 4765.
3. See reference 7 in preceding paper.
4. Stevenart-De Mesmaeker, N.; Merenyi, R.; Vieke, H.G., *Tetrahedron Lett.*, 1987, **28**, 2591. Yamamoto, M.; Tanaka, S.; Naruchi, K.; Kazutoshi, K., *Synthesis*, 1982, **10**, 8512. Loeffler, L.J.; Sajadi, Z.; Hall, I.H., *J. Med. Chem.*, 1977, **12**, 1578.
5. Molander, G.A.; McKie, J.A., *J. Org. Chem.*, 1992, **57**, 3132.
6. Curran, D.P.; Wolin, R.L., *Synlett.*, 1991, **5**, 317.
7. Molander, G.A.; La Belle, B.E.; Hahn, G., *J. Org. Chem.*, 1986, **51**, 5259.

8. Ashworth, P.J.; Whitham, G.H.; Whiting, M.C., *J. Chem. Soc.*, 1957, 4633.
9. Komarov, N.V.; Shostakovskii, M.F., *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1960, 1300.
10. Miller, R.B., *Syn. Comm.*, 1972, 2(5), 267.

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