Asymmetric Radical Cyclization With Pyroglutamate: Synthesis of 7-Substituted Pyrrolizidinones

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Chiral, non-racemic *N*-(2-iodoethyl)-5-vinylpyrrolidin-2-ones have been synthesized and then cyclized with tributyltin hydride and azoisobutyronitrile (AIBN) to produce chiral, non-racemic pyrrolizidin-2-ones, with high diastereoselectivity. Reduction of the lactam moiety provides a facile route to naturally occurring pyrrolizidine alkaloids.

Pyrrolizidine alkaloids occur in more than 40 genera of plants, particularly in the genera *Senecio* and *Crotalaria* and have a wide range of biological activities.[1] The most common synthetic route is that adapted by Robins and Sakdarat,[2] which involves nucleophilic condensations *via* a L-proline precursor. This is similar to the route employed by Geissman and Waiss in the first synthesis of a necine base, racemic retronecine, in 1962.[3] The key intermediate in this synthesis was a lactone that has been used in a number of syntheses of both chiral racemic and chiral non-racemic alkaloids.[4] This intermediate can be prepared from L-proline in 11 steps[5] or from malic acid in 8 steps.[6] Reuger and Benn synthesized trachelanthamidine, isoretronecanol, supinidine, petasinecine and its epimer *via* a Dieckmann condensation, with good enantioselectivities (80–94% ee's).[7] Malic acid derivatives have attracted much attention in the asymmetric syntheses of pyrrolizidines because both antipodes of malic acid are available in enantiomerically pure form. Chamberlin and Chung[8] prepared a chiral nonracemic succinimide precursor from malic acid that was selectively reduced and cyclized *via* an intermolecular acyliminium ion-ketone dithioacetal to form a pyrrolizidin-3-one thioacetal. This intermediate was converted into all seven naturally occurring saturated and unsaturated diols. There are a few asymmetric syntheses using carbohydrates as a starting material for pyrrolizidines,[4] but these generally target the triol pyrrolizidines. Additionally, carbohydrates have been converted into the Geissman–Waiss lactone in 11 steps, leading to formal syntheses of four diol necine bases.[9]

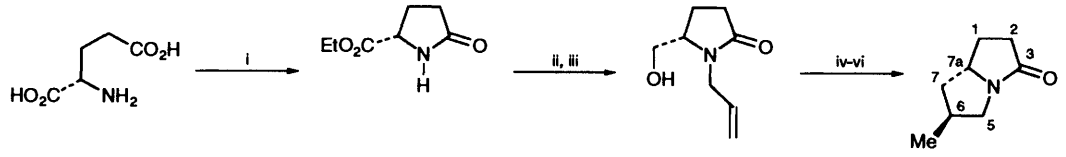
A completely different synthetic strategy is illustrated by Hart's radical cyclization of achiral 1-butenyl-5-thiophenylpyrrolidin-2-ones, which were cylized to give a mixture of pyrrolizidines, indolizidines as well as the lactam resulting from hydrogen transfer in a total yield of 84%.[10] The pyrrolizidine derivative showed high stereoselectivity (> 10:1) in the cyclization step. In more recent work, Hart reported the asymmetric synthesis[11] of swainsonine,[12] but this required the preparation of a chiral non-racemic lactam precursor.[11] Livinghouse used prolinol as a precursor for the asymmetric synthesis of pyrrolizidine alkaloids[13] *via* radical cyclization of a 2-vinyl-L-prolinol derivative, initiated photochemically in the presence of $(Bu_3Sn)_2$. High diastereoselectivity was observed in the cyclization reaction (30:1). Attempted cyclization using tributyltin hydride led to a 2:1 mixture of the hydrogen-transfer product and a perhydroindolone (80% combined yield).[13]

Work in our laboratory previously established the methodology for radical cyclization using 6-methylpyrrolizidin-3-one as a model for later syntheses of natural products.[14] In this work, ethyl pyroglutamate **2** (derived from L-glutamic acid **1**) was used as the chiral non-racemic building block such that the original stereogenic centre was retained (as the bridgehead hydrogen in **4**) and the C-5 centre in **2** imparted diastereoselectivity into the ring-forming reaction.[14] Ethyl pyroglutamate, **2** was converted into the *N*-allyl or -alkenyl derivative with KOH and phase-transfer catalysts using Takahata's method[15] for preparing *N*-alkyllactams. Reduction of **2** with $LiAlH_4$–SiO_2, Hojo's method,[16] gave the corresponding alcohol **3**. Reaction with methanesulfonyl chloride and triethylamine at −78 °C yielded the mesylate and Finkelstein exchange with NaI in acetone led to an *N*-allyl iodomethyl lactam with retention of the *S* configuration at C-5. Treatment of this iodoalkene with AIBN and Bu_3SnH in refluxing benzene led to a 70% yield of **4** with high diastereoselectivity for the *exo*-methyl diastereoisomer shown. We prepared a variety of chiral non-racemic pyrrolizidinone derivatives by this method.[14] The diastereoselectivity was greater than 50:1 (no other isomer is observable by NMR. Knapp has also used pyroglutamate **2** as a precursor for the asymmetric synthesis of pyrrolizidine alkaloids *via* radical cyclization.[17]

Our prior work demonstrated the viability of using pyroglutamate as an asymmetric precursor to pyrrolizidine alkaloids. The preparation of 'natural' pyrrolizidine alkaloids which are functionalized at C-1 and C-7 rather than C-6 (see **4**), required that the point of attack for the cyclization technique be 'reversed' relative to the reaction of **3**. Rather than the 5-hydroxymethyl group with an *N*-allyl moiety as in **3** a 'reverse' cyclization required an *N*-halogenoethyl group and a vinyl group at C-5 (such as **10**). The key intermediate for our synthesis was (*S*)-5-vinylpyrrolidin-2-one **8**. Metcalf[18] as well as Frieben and Fritz[19] prepared this compound in their synthesis of 4-aminohex-5-enoic acid, a potent inhibitor of 4-aminobutyrate-2-oxoglutarate aminotransferase (GABA aminotransferase, GABA-T), a mitochondrial enzyme found in synaptic neurons.[20] We prepared **8** in five synthetic steps from **2**.[21] Reaction of **2** with butanal (P_2O_5 in refluxing toluene)[22] to give (*S*)-5-hydroxymethylpyrrolidin-2-one was followed by reduction with $NaBH_4$ to give **5** in 66% yield. Moffatt oxidation[23] gave aldehyde **6** in 83% yield, allowing the subsequent Wittig olefination reaction to give **7** in 69% yield. Aqueous acid hydrolysis removed the butenyl protecting group[24] and opened the lactam ring to the amino acid. Basification and heating, without isolation of the intermediate products, afforded the final target **8** in 58% yield from **7**. This sequence gave **8** in 22% overall yield from **2**.

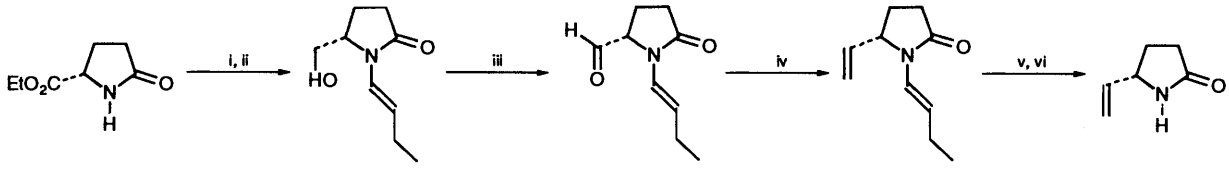
With the desired alkenyl group incorporated at C-5, we targetted incorporation of the *N*-halogenoethyl moiety. Although both *N*-(2-chloroethyl)-) and *N*-(2-bromoethyl)pyrrolidin-2-one were known compounds,[25] the techniques used to prepare these compounds gave poor results with our 5-substituted

† Taken, in part, from the Ph.D thesis of P. F. K., 1991.



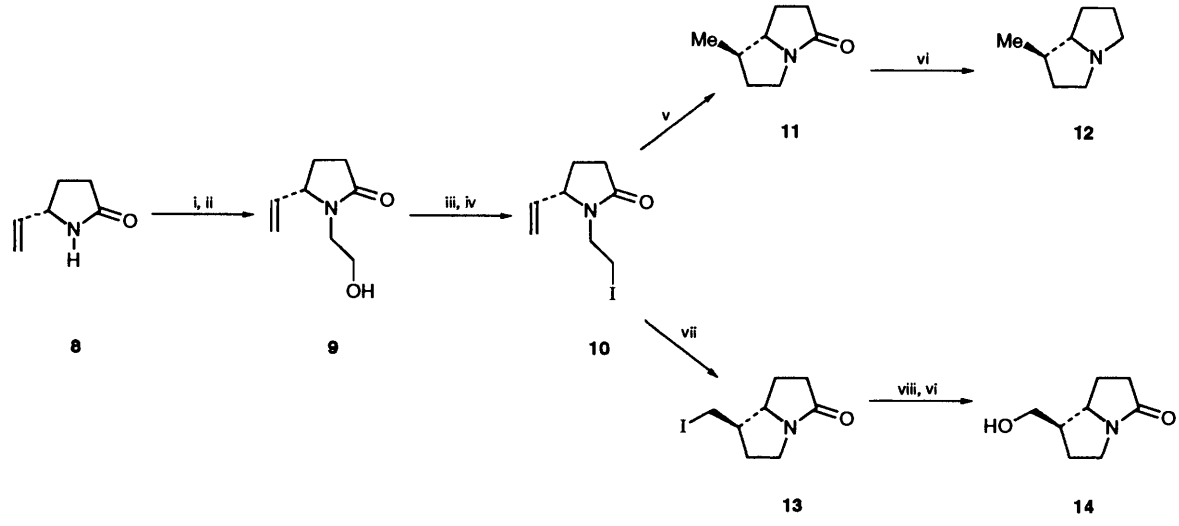
1 2 3 4

Scheme 1 *Reagents and conditions:* i, $SOCl_2$, EtOH; ii, CH_2=$CHCH_2Br$/KOH/Bu_4NBr/THF/sonication; iii, $LiAlH_4/SiO_2$; iv, MsCl/Py; v, NaI/acetone; vi, AIBN, Bu_3SnH, PhH, reflux



2 5 6 7 8

Scheme 2 *Reagents and conditions:* i, butanal, P_2O_5, PhMe; ii, $LiBH_4$; iii, DCC, DMSO, H^+, heat; iv, Ph_3PCH_3/Bu^{t}OK, THF; v, 1 mol dm^{-3} HCl; vi, aq. NaOH, 95 °C



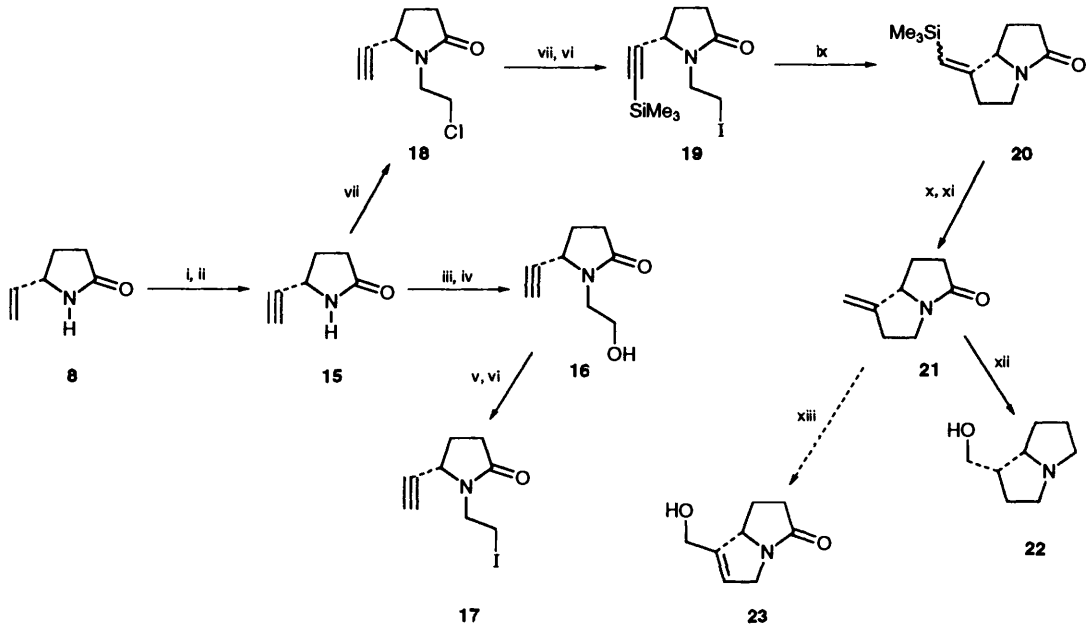
8 9 10 11 12 13 14

Scheme 3 *Reagents and conditions:* i, $BrCH_2CO_2Et$/KOH/THF; ii, $NaBH_4$; iii, MsCl/NEt_3; iv, NaI/acetone; v, AIBN/Bu_3SnH/PhH; vi, $LiAlH_4$; vii, $(Bu_3Sn)_2$/*hv*/EtI; viii, CsO_2CEt

pyrrolidin-2-one derivatives. We found that the most direct route to the *N*-(2-hydroxyethyl)pyrrolidin-2-one derivative, the precursor to the desired halogenoethyl derivative, was reaction of **8** with ethyl bromoacetate to give (5*S*)-vinyl-*N*-(ethoxycarbonylmethyl)pyrrolidin-2-one followed by reduction of the ester moiety with $NaBH_4$. This sequence converted **8** into **9** in 80% overall yield. This is a very efficient route to *N*-(hydroxyethyl) lactams. The next step was conversion of the alcohol into an iodide **10** by initial mesylation to (5*S*)-vinyl-*N*-(2-mesyloxyethyl)pyrrolidin-2-one and followed by Finkelstein exchange (45% yield for both steps). Radical cyclization of **10** with tributyltin hydride and AIBN in refluxing benzene gave the pyrrolizidinone **11** in 87% yield. The selectivity for the *exo*-methyl diastereoisomer shown (**11**) was >60:1 as determined by GC/MS using pyrrolidin-2-one as an internal standard. Reduction of the lactam moiety with $LiAlH_4$ produced (−)-heliotridane **12** in 80% yield.

A simple modification of this sequence allowed us to prepare a second naturally occurring pyrrolizidine alkaloid, (−)-trachelanthamidine **14**. Radical cyclization of **10** with $(Bu_3Sn)_2$ with a sunlamp (Livinghouse's conditions),[13] in the presence of iodoethane as an iodine transfer agent, led to an 81% yield of **13**. Again using Livinghouse's method,[13] treatment of **13** with cesium propionate[26] and reduction with $LiAlH_4$ gave **14** in 75% yield.

The next step in our synthetic strategy was to manipulate the stereochemistry at C-7 in the pyrrolizidine alkaloid product. This required the preparation of 7-methylenepyrrolidin-2-one **21** which Simpkins[27] showed gave (−)-isoretronecanol upon hydroboration. Our first key reaction was the conversion of the vinyl group in **8** to an ethynyl group. Bromination of **8** followed by treatment with an excess of potassium *tert*-butoxide in *tert*-butyl alcohol gave an 86% yield of (*S*)-5-ethynylpyrrolidin-2-one **15**. We then converted **15** into the hydroxymethyl derivative **16** by reaction with ethyl bromoacetate [63% yield of (5*S*)-ethynyl-*N*-(ethoxycarbonylmethyl)pyrrolidin-2-one] and reduction with $NaBH_4$ (77% yield). Mesylation to (5*S*)-ethynyl-*N*-(2-mesyloxyethyl)pyrrolidin-2-one and Finkelstein exchange (60% overall) gave **17** but several attempts at radical cyclization failed to produce **21** in significant yields. We therefore modified the reaction sequence to prepare a silyl-protected alkynyl derivative, similar to the strategy used by Hart.[10a,b] We found that the presence of the alkynyl group at C-5 in **15** greatly accelerated the rate of *N*-alkylations. All previous attempts to bring about the reaction of 1-bromo-2-chloroethane and various lactams failed to give the alkylation product. Reaction of **15** with this dihalide, however, gave **18** in 70% isolated yield. Treatment of this with butyllithium and quenching with iodotrimethylsilane gave (2-chloroethyl)-5-(trimethylsilylethynyl)pyrrolidin-2-one in 85% yield and



Scheme 4 *Reagents and conditions:* i, Br_2; ii, Bu^{t}OK/Bu^{t}OH; iii, $BrCH_2CO_2Et$/KOH/THF; iv, $NaBH_4$; v, MsCl/NEt_3; vi, NaI/acetone; vii, $BrCH_2CH_2Cl$/THF; viii, BuLi/Me_3SiCl; ix, AIBN/Bu_3SnH/PhH; x, *p*-TsOH; xi, AcOH/CH_2Cl_2/DMAP; xii, BH_3·SMe_2; xiii, refs. 11 and 28

Finkelstein exchange gave the iodide **19** in 79% yield. Radical cyclization now proceeds smoothly with AIBN/Bu_3SnH/benzene to give **20** in 80% yield. When **20** was treated with toluene-*p*-sulfonic acid in aqueous acetonitrile, followed by reaction with acetic acid in CH_2Cl_2 and dimethylaminopyridine, **21** was isolated in 82% yield. When **21** was treated with borane (1 mol dm^{-3} in THF) and then oxidized (H_2O_2, NaOH), the alkene was converted into the hydroxymethyl derivative with simultaneous reduction of the lactam carbonyl to give (−)-isoretronecanol **22** directly in 63% yield. The synthesis of **21** also constitutes a formal synthesis of supinidine **23**, which Hart prepared from chiral racemic **21** in 39% yield and in four steps.[11] Kano and co-workers[28] also prepared supinidine from **21** in 68% yield.

These syntheses have shown that pyroglutamate is a useful chiral nonracemic precursor to chiral nonracemic pyrrolizidine alkaloids. Both the vinyl derivative **8** and the ethynyl derivative **15** are interesting and highly useful synthetic intermediates for asymmetric synthesis. We have prepared several naturally occurring pyrrolizidine alkaloids by essentially one synthetic method. The lactam ring provides an internally protected molecule allowing both the radical cyclization and also manipulation of the various functional groups at C-7 in the pyrrolizidinone product. We believe this is an important addition to the growing field of radical cyclization techniques and to the asymmetric synthesis of pyrrolizidine alkaloids.

Experimental

M.p.s were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Infrared Spectrophotometer Model 283 and recorded in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were taken in deuteriochloroform on a IBM 270 MHz Spectrometer at 270.13 MHz and 67.3 MHz respectively and reported in ppm downfield from tetramethylsilane (TMS) as an internal standard; *J* values are recorded in Hz. Multiplicities were determined either by off-resonance decoupling or INEPT experiments. High-resolution mass spectra were measured on an AEI Mass Spectrum-902 mass spectrometer and are accurate to ± 5 ppm. Optical activities $[\alpha]_D$ were measured with an O.C. Rudolph polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Apparatus for experiments requiring anhydrous conditions were flame dried, allowed to cool in a desiccator over calcium chloride and flushed with argon prior to use. Sonication was done in a Bransonic 220 cleaning bath that had been previously mapped for optimum sonication by floating aluminium foil 1 cm above the floor of the bath and recording where the aluminium had been disintegrated. This procedure was repeated with the aluminium foil suspended 1 cm below the surface of the water in the bath.

(S)-(+)-5-*Ethoxycarbonylpyrrolidin*-2-*one* **2**.—The procedure of Adkins and Billica[29b] was modified by adding freshly distilled thionyl chloride (60 cm^3, 0.8 mol) to a suspension of L-glutamic acid **1** (51.2 g, 348 mmol) in commercial absolute ethanol (500 cm^3), cooled in an ice-bath. The solution was stirred at room temperature for 1 h and refluxed for 0.5 h. Ethanol was removed under reduced pressure and the viscous oil was heated under reduced pressure (140–155 °C, 3 mmHg) for 3 h. Kugelrohr distillation gave **2** as colourless needles (47.8 g, 303 mmol, 87%), m.p. 50–51 °C (lit.,[29a] m.p. 51–52 °C); H $\delta_H(CDCl_3)$ 7.2 (1 H, br), 4.1 (3 H, m), 2.3 (4 H, m) and 1.3 (3 H, t); $\delta_C(CDCl_3)$ 180 (s), 152 (s), 61.6 (t), 56 (d), 29.5 (t), 22 (t) and 14.4 (q); ν_{max}(neat)/cm^{-1} 3230br, 1740s, 1700s, 1200s, 1100m, 1040m and 740br; *m*/*z* (rel. int.) 157(14), 135(8), 129(80), 127 (6), 99 (8), 84 (10), 83 (100), 73 (8), 56 (44) and 55 (6); $[\alpha]_D^{25}$ +2.4 (*c* 10, EtOH).

(−)-N-(*But*-1-*enyl*)-5-*hydroxymethylpyrrolidin*-2-*one* **5**.—The ester **24** (0.43 g, 2.0 mmol) was dissolved in ethanol (5 cm^3), and sodium borohydride (0.16 g, 2.1 mmol) in ethanol (5 cm^3) was added slowly at 0 °C to the solution. After 18 h at ambient temperature, the solution was quenched with acetone at 0 °C and stirred for 1 h. The mixture was then filtered and evaporated and column chromatography (silica, ether) of the residue gave **5** (0.27 g, 1.7 mmol, 85%); $\delta_H(CDCl_3)$ 1.05 (3 H, t), 2.45 (4 H, m), 3.72 (1 H, m), 3.90 (1 H, m), 4.20 (1 H, s), 5.25 (1 H, m) and 6.71 (1 H, d); $\delta_C(CDCl_3)$ 14.4 (q), 21.7 (t), 21.74 (t), 23.6 (t), 30.8 (t), 58.6 (d), 61.2 (t), 115.1 (d), 121.8 (d) and 174.0 (s); ν_{max}(neat)/cm^{-1} 3400br, 1680s, 1410m, 1280m and 1110m; *m*/*z* (rel. int.) 169 (22), 138 (100), 126 (5), 110 (8), 96 (12), 84 (14), 70 (18) and 55 (25) [Found: *m*/*z* (HRMS) 169.1095 (± 0.9 mmu). Calc. for $C_9H_{15}NO_2$ 169.1104]; $[\alpha]_D^{25}$ −2.0 (*c* 0.056, CH_2Cl_2).

(−)-N-(*But*-1-*enyl*)-5-*formylpyrrolidin*-2-*one* **6**.—The alcohol **5** (0.37 g, 2.2 mmol) was dissolved in dry DMSO (freshly distilled over CaH_2; 10 cm^3) and dry benzene (freshly distilled from $LiAlH_4$; 10 cm^3). Freshly distilled pyridine (0.173 cm^3, 2.2 mmol), trifluoroacetic acid (0.083 cm^3 (1.1 mmol) and dry 1,3-dicyclohexylcarbodiimide (DCC) (must be freshly Kugelrohr distilled at 145 °C, 2 mm Hg; 1.33 g, 6.3 mmol) were added in that order. The tightly stoppered solution was stirred under Ar for 14 h and then diluted with ether (100 cm^3), filtered and extracted (3 × 10 cm^3) with water. The combined aqueous layers were extracted with CH_2Cl_2 (×3), and the combined organic fractions were dried ($MgSO_4$), evaporated under reduced pressure and the residue dried *in vacuo* for several hours to give **6** (0.30 g, 1.8 mmol, 83%) which was used without further purification; $\delta_H(CDCl_3)$ 1.05 (3 H, t), 2.11 (2 H, m), 2.45 (2 H, m), 4.30 (1 H, m), 5.93 (1 H, m), 6.85 (1 H, d) and 9.6 (1 H, d); $\delta_C(CDCl_3)$ 14.3 (q), 19.7 (t), 23.3 (t), 29.8 (t), 63.9 (d), 115.3 (d), 122.4 (d), 173.0 (s) and 200 (d); ν_{max}(neat)/cm^{-1} 3100–2800s, 1730s, 1680s, 1410m, 1070m and 950m; *m*/*z* (rel. int.) 167 (16), 138 (100), 124 (2), 110 (7), 95 (6), 84 (8), 68 (12) and 55 (21) [Found: *m*/*z* (HRMS) 167.0939 (±0.8 mmu). Calc. for $C_9H_{13}NO_2$: 167.0947].

(−)-N-(*But*-1-*enyl*)-5-*vinylpyrrolidin*-2-*one* **7**.—Freshly sublimed potassium *tert*-butoxide (0.74 g, 6.6 mmol) was added to methyltriphenylphosphonium bromide (2.4 g, 6.6 mmol) in dry THF (freshly distilled over Na; 10 cm^3) and stirred at room temperature for 20 min. The aldehyde **6** (estimate quantity from the above reaction, 2.2 mmol) dissolved in dry THF (10 cm^3), was then slowly added *via* a syringe to give a bright yellow solution which was stirred at room temperature under Ar for 12 h. After this, the reaction was quenched with water (10 cm^3) and extracted with ether (×3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give a yellow oil which was purified by column chromatography (silica, ether R_F 0.6) to give **7** (0.25 g, 1.5 mmol, 69%); $\delta_H(CDCl_3)$ 0.91 (3 H, t), 2.45 (6 H, m), 4.30 (1 H, s), 5.25 (3 H, m), 5.82 (1 H, m) and 6.81 (1 H, d); $\delta_C(CDCl_3)$ 14.5 (q), 23.6 (t), 25.8 (t), 29.7 (t), 60.0 (d), 115.8 (d), 166.0 (d), 121.9 (d), 136.7 (d) and 174.0 (s); ν_{max}(neat)/cm^{-1} 2900br, 1680s, 1410m, 1280m and 1110m; *m*/*z* (rel. int.) 165 (32), 151 (6), 150 (52), 138 (12), 137 (55), 122 (17), 110 (28), 108 (22), 97 (10), 95 (18), 84 (16), 82 (35), 68 (38), 67 (65), 56 (25), 55 (33), 54 (39), 53 (23) and 48 (3) [Found: *m*/*z* (HRMS) 165.1162 (±0.7 mmu). Calc. for $C_{10}H_{15}NO$: 165.1154]; $[\alpha]_D^{25}$ −46.3 (*c* 0.0320, CH_2Cl_2).

(S)-5-*Vinylpyrrolidin*-2-*one* **8**.—Aqueous HCl (10%; 10 cm^3) was added to the pyrrolidin-2-one **7** (252 mg, 1.53 mmol) and the mixture heated to 90 °C over a steam-bath for 5 h. The resulting clear solution was evaporated under reduced pressure and the residue dried *in vacuo*. The resulting yellow oil was dissolved in water and the solution treated with charcoal and filtered. Rotary evaporation of the solution and chromatography (SiO_2) of the residue gave crystalline (*S*)-4-aminohex-5-enoic acid[21] (160 mg, 0.160 g, 1.24 mmol, 81%), m.p. 207–209 °C (lit.,[30b] m.p. 208); $[\alpha]_D^{23}$ = +12.5 (pH = 6.6, *c* 0.020, H_2O) {lit.,[30a] $[\alpha]_D^{23}$ = +12.3 ±0.3, *c* = 0.200, H_2O); $\delta_H(CDCl_3)$ 1.8 (3 H, t), 2.11 (2 H, m), 2.45 (2 H, m), 4.30 (1 H, m), 5.93 (1 H, m), 6.85 (1 H, d) and 9.6 (1 H, d); $\delta_C(CDCl_3)$ 14.3 (q), 19.7 (t), 23.3 (t), 29.8 (t), 63.9 (d), 115.3 (d), 122.4 (d), 173.0 (s) and 200 (d); ν_{max}(neat)/cm^{-1} 3100–2800s, 1730s, 1680s, 1410m, 1070m and 950m.

A stirred suspension of (*S*)-4-aminohex-5-enoic acid (19.7 mg, 0.153 mmol) in methanol (5 cm^3) was treated with thionyl chloride (0.01 cm^3) with ice cooling. The mixture was then heated under reflux for 3.5 h, after which evaporation of solvent gave an oil which was dissolved in water (5 cm^3). Sodium carbonate was added to the solution and the resulting mixture was extracted with CH_2Cl_2 (×3). Drying and evaporation of the combined extracts gave the methyl ester as a yellow oil which was heated in refluxing toluene for 40 h. Evaporation of the mixture and chromatography of the residue gave (*S*)-5-vinylpyrrolidin-2-one **8**[20,21] as a yellow oil (12.0 mg, 0.108 mmol, 71%); $\delta_H(CDCl_3)$ 1.05 (3 H, t), 2.11 (2 H, m), 2.45 (2 H, m), 4.30 (1 H, m), 5.93 (1 H, m), 6.85 (1 H, d) and 9.6 (1 H, d); $\delta_C(CDCl_3)$ 14.3 (q), 19.7 (t), 23.3 (t), 29.8 (t), 63.9 (d), 115.3 (d), 122.4 (d), 173.4 (s) and 200 (d); ν_{max}(neat)/cm^{-1} 3100–2800s, 1730s, 1680s, 1410m, 1070m and 950m cm^{-1}.

(S)-(+)-1-(2-*Hydroxyethyl*)-5-*vinylpyrrolidin*-2-*one* **9**.—The ester **25** (1.63 g, 8.25 mmol) was dissolved in ethanol (15 cm^3) and sodium borohydride (0.630 g, 16.5 mmol) in ethanol (15 cm^3) was added slowly to the solution. After 12 h at ambient temperature, the solution was quenched with acetone and stirred for 1 h. After filtration and evaporation of the mixture, column chromatography (silica, ether) of the residue gave the alcohol **9** (1.03 g, 6.62 mmol, 80%); R_F 0.090 (ether); $\delta_H(CDCl_3)$ 1.79 (m, 1 H), 2.42 (m, 3 H), 3.66 (m, 3 H), 4.20 (m, 3 H), 5.18 (m, 2 H) and 5.58 (m, 1 H); $\delta_C(CDCl_3)$ 25.6 (t), 30.0 (t), 43.7 (t), 59.9 (d), 62.5 (t), 118.4 (t), 137.6 (d) and 176.5 (s); ν_{max}(neat)/cm^{-1} 3380, 3089, 2972, 1922, 1666, 1422, 1364, 1183, 1054 and 935; *m*/*z* (rel. int.) 197 (27), 152 (8), 151 (17), 125 (13), 124 (100), 123 (12), 110 (32), 96 (24), 95 (19), 82 (13), 81 (17), 68 (18), 67 (42), 55 (11), 54 (11), 42 (14) and 41 (46) [Found: *m*/*z* (HRMS) 155.0940. Calc. for $C_8H_{13}NO_2$: 155.0946]; $[\alpha]_D^{25}$ +45.3 (*c* 0.0114, CH_2Cl_2).

(S)-1-*Iodoethyl*-5-*vinylpyrrolidin*-2-*one* **10**.—The mesylate **26** (0.210 g, 0.900 mmol), NaI (oven dried *in vacuo*; 0.4 g) and anhydrous acetone (8 cm^3) were stirred for 12 h under argon and then refluxed for 1 h. The solution was filtered, the solids washed with acetone and the solvent evaporated under reduced pressure to yield a yellow oil. Ether was added to the oil and the resulting solution was washed with water, saturated aqueous sodium sulfite and brine. After evaporation of solution under reduced pressure, column chromatography (silica/ether) of the residue gave **10** (0.12 g, 0.80 mmol, 89%), R_F 0.42 (ether); $\delta_H(CDCl_3)$ 1.82 (m, 1 H), 2.38 (m, 3 H), 3.25 (m, 3 H), 3.84 (m, 1 H), 4.14 (m, 1 H), 5.31 (m, 2 H) and 5.68 (m, 1 H); $\delta_C(CDCl_3)$ 0.8 (t), 25.6 (t), 29.9 (t), 43.3 (t), 61.7 (d), 118.6 (t), 137.4 (d) and 176 (s); ν_{max}(neat)/cm $^{-1}$ 3039, 2940, 2900, 1665, 1388, 1240, 1160, 1118, 972 and 910; *m*/*z* (rel. int.) 265 (1), 236 (1), 209 (12), 155 (11), 139 (10), 138 (100), 124 (22), 95 (13), 82 (8), 70 (8), 68 (9), 67 (37), 56 (10), 55 (16), 54 (16), 42 (15), 41 (30) and 39 (22) [Found: *m*/*z* (HRMS) 264.9968. Calc. for $C_8H_{12}INO$: 264.9966]; $[\alpha]_D^{25}$ +29 (*c* 0.040, CH_2Cl_2).

(S)-(−)-7-*Methylhexahydropyrrolizin*-3-*one* **11**.—The pyrrolidin-2-one **10** (0.092 g, 0.35 mmol), tributyltin hydride (0.12 cm^3, 0.42 mmol) and a catalytic amount of AIBN (2 mg) in dry, degassed benzene (60 cm^3) were heated to reflux for 6 h under argon. Evaporation of solvent from the mixture and column chromatography (silica/ether) of the residue gave the title compound **11**[10] (0.042 g, 0.31 mmol, 87%); R_F 0.30 (ether); $\delta_H(CDCl_3)$ 1.04 (d, 3 H, *J* 6.13), 1.70 (m, 2 H), 2.26 (m, 2 H), 2.45 (m, 2 H), 2.70 (m, 2 H), 3.16 (dd, 1 H) and 3.48 (m, 1 H); $\delta_C(CDCl_3)$ 15.4 (q), 25.3 (d), 35.0 (t), 35.6 (t), 40.7 (t), 41.0 (t), 68.3 (d) and 174.8; *m*/*z* (rel. int.) 140 (3), 139 (35), 138 (4), 124 (1), 110 (1), 98 (7), 97 (100), 84 (8), 69 (56), 68 (24), 67 (4), 56 (12), 55 (31) and 54 (9); $[\alpha]_D^{25}$ −10.2 (*c* 0.102, CH_2Cl_2).

(−)-*Heliotridane* **12**.—To a stirred solution of the hexapyrrolizinone **11** (0.025 g, 0.18 mmol) in dry THF (4 cm^3) was added $LiAlH_4$ (0.029 g, 0.73 mmol) in one portion. The mixture was heated at reflux for 30 min and then diluted with water, 10% aqueous NaOH and water. The resulting slurry was stirred for

5 min and then filtered through Celite. The filtrate was concentrated under reduced pressure to give **18** (0.019 g, 0.15 mmol, 84%); $\delta_H(CDCl_3)$ 1.05 (t, 3 H), 1.93–2.75 (m, 8 H) and 2.77–3.27 (m, 4 H); ν_{max}(neat)/cm^{-1} 2900m, 1455m, 1375m and 1220m; *m/z* (rel. int.) 123 (20) and 83 (100); $[\alpha]_D^{23}$ −90.0 (*c* 0.033, EtOH) {lit.,[32] $[\alpha]_D^{34}$ −91.3, neat}.

(S)-(−)-*Iodomethylpyrrolizin*-3-*one* **13**.—An oven-dried flask was charged with the pyrrolidin-2-one **10** (0.493 g, 1.86 mmol), benzene (50 cm^3), iodoethane (0.52 cm^3, 6.5 mmol) and $(Bu_3Sn)_2$ (0.52 cm^3, 0.95 mmol). The resulting solution was stirred and irradiated with a 275-W sunlamp for 6 h, whereupon TLC indicated complete consumption of starting material. Benzene was removed from the mixture by evaporation under reduced pressure, and the residue was subjected to column chromatography (silica/ether) to provide the title compound **13** (0.400 g, 1.51 mmol, 81%); R_F 0.30 (ether); $\delta_H(CDCl_3)$ 1.25 (m, 1 H), 1.87 (m, 3 H), 2.40 (m, 3 H), 2.69 (m, 1 H, 3.19 (d, 2 H) and 3.63 (m, 2 H); $\delta_C(CDCl_3)$ 5.1 (t), 26.8 (t), 34.5 (t), 35.1 (t), 47.5 (t), 67.3 (d) and 174 (s); ν_{max}(neat)/cm^{-1} 3446br, 2928m, 2888m, 1683s, 1456m, 1417m, 1337w, 1280m, 1186m, 1047w, 803w and 667w; *m/z* (rel. int.) 265 (1), 210 (1), 155 (2), 139 (8), 138 (100), 110 (10), 84 (25), 68 (8), 55 (61), 54 (11) and 41 (33) [Found: *m/z* (HRMS) 264.9953. Calc. for $C_8H_{12}NOI$: 264.9964]; $[\alpha]_D^{25}$ −9 (*c* 0.020, EtOH).

(−)-*Tetrachelanthamide* **14**.—Cesium carbonate (5 mmol) was dissolved in dry methanol (40 cm^3) and to the solution was added propionic acid (10 cm^3, 9.92 g, 134 mmol) dissolved in dry methanol. The mixture was stirred for 30 min after which the methanol was removed under reduced pressure to afford a white powder. This was collected on a glass filter and washed repeatedly with ether until no propionic acid could be detected in the washings.

The iodide **13** (0.072 g, 0.27 mmol) was dissolved in the appropriate amount of DMF (5 cm^3) (solubility of Cs propionate = 12.4 × 10^{-2} mol dm^{-3}) and cesium propionate (0.075 g, 0.36 mmol) was then added in solid form to the solution. The reaction mixture was stirred vigorously and brought to 60 °C at which it was stored for 24 h. After addition of brine to the reaction mixture, the aqueous layer was separated and extracted with ether (× 3). The combined extracts were then dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography (silica/ether).

To a stirred solution of this crude product (0.055 g, 0.26 mmol) in dry THF (6 cm^3) was added $LiAlH_4$ (0.050 g, 1.3 mmol) in one portion. The mixture was heated at reflux for 30 min and then diluted with water, 10% aqueous NaOH and water. The resulting slurry was stirred for 5 min and filtered through Celite. The filtrate was concentrated under reduced pressure to give **14** (0.028 g, 0.20 mmol, 75%); $\delta_H(CDCl_3)$ 1.6–2.1 (m, 9 H), 2.61 (m, 2 H), 3.11 (m, 1 H) and 3.8 (br s, 1 H); $\delta_C(CDCl_3)$ 25.8 (t), 30.2 (t), 32.1 (t), 48.7 (d), 54.9, 56.9, 65.3 and 67.8; ν_{max}(neat)/cm^{-1} 3340br; *m/z* (rel. int.) 141 (25), 140 (25), 124 (20), 110 (25) and 83 (100); $[\alpha]_D^{23}$ −14 (*c* 0.063, EtOH) (lit.,[2b,13] $[\alpha]_D^{23}$ −13.5, *c* 2, EtOH).

(S)-(+)-5-*Ethynylpyrrolidin*-2-*one* **15**.—To a solution of the pyrrolidin-2-one **8** (1.41 g, 12.7 mmol) in carbon tetrachloride (20 cm^3) was added a solution of bromine (0.74 cm^3, 12.7 mmol) in carbon tetrachloride (6 cm^3) with ice cooling and stirring. During this addition, a viscous oil separated. After the addition, stirring was continued for 1 h at room temperature. The solvent was removed from the mixture under reduced pressure, the residue was dissolved in CH_2Cl_2 and the solution washed with 10% aqueous sodium sulfite until nearly colourless. The aqueous phase was made basic with solid sodium carbonate and extracted with CH_2Cl_2 (× 2). The combined extracts were dried and evaporated to give an oil which was purified by chromatography to yield 5-(1,2-dibromoethyl)pyrrolidin-2-one (3.23 g, 11.9 mmol, 94%, silica/ether).[30b]

To a suspension of potassium *tert*-butoxide (6.5 g, 58 mmol) in dry THF (10 cm^3) cooled to −78 °C, a solution of 5-(1-2-dibromoethyl)pyrrolidin-2-one (2.65 g, 9.8 mmol) in THF was added slowly *via* a syringe over 30 min. The mixture was allowed to warm to −20 °C and then poured into an ice-cold solution of 25% aqueous acetic acid (15 cm^3) and diluted with ether (50 cm^3). The aqueous layer was separated, made basic with sodium carbonate and extracted with CH_2Cl_2 (× 2). The combined extracts were dried ($MgSO_4$) and evaporated and the product was purified by chromatography (silica/ether) to give the title compound **15** as a yellow oil (8.95 mmol, 92%);[30b] R_F 0.25 (ether); $\delta_H(CDCl_3)$ 1.93–2.73 (5 H, m), 4.40 (1 H, m) and 7.95 (1 H, br s); $[\alpha]_D^{25}$ +15.82 (*c* 3.1, EtOH).[30b]

(S)-(+)-5-*Ethynyl*-1-(2-*hydroxyethylpyrrolidin*-2-*one* **16**.—The ester **27** (1.0 g, 5.1 mmol) was dissolved in ethanol (25 cm^3) and sodium borohydride (0.39 g, 10 mmol) in ethanol (25 cm^3) was added slowly to the solution. After 12 h at ambient temperature, the solution was quenched with acetone and stirred for 1 h. Filtration of the solution followed by evaporation and column chromatography (silica ether) of the residue gave the alcohol **16** (0.60 g, 4.0 mmol, 77%); R_F 0.21 (ether); $\delta_H(CDCl_3)$ 2.13 (1 H, m), 2.43 (4 H, m), 3.28 (1 H, m), 3.58 (1 H, m), 3.67 (2 H, m), 4.01 (1 H, br) and 4.52 (1 H, m); $\delta_C(CDCl_3)$ 26.1 (t), 43.9 (d), 49.9 (t), 60.1 (t), 73.6 (d), 81.2 (s) and 175.5 (s); ν_{max}(neat)/cm^{-1} 3390, 2900, 2855, 2110, 1675, 1460, 1432, 1355, 1275, 1197, 1086, 880 and 695; *m/z* (rel. int.) 153 (1), 152 (1), 136 (10), 123 (11), 122 (100), 110 (35), 94 (12), 80 (20), 77 (9), 68 (34), 67 (33), 65 (66) and 55 (25); $[\alpha]_D^{25}$ +9.5 (*c* 0.121, CH_2Cl_2).

(S)-(+)-5-*Ethynyl*-1-(2-*iodoethyl*)*pyrrolidin*-2-*one* **17**.—The mesylate **28** (0.66 g, 2.8 mmol) and NaI (3 g) in dry acetone (50 cm^3) were stirred for 16 h and refluxed for 1 h. Filtration and evaporation of solvent from the mixture followed by chromatography (silica/ether) of the residue gave the title compound **17** as a yellow oil (2.4 mmol, 85%): R_F 0.55 (ether); $\delta_H(CDCl_3)$ 2.14 (1 H, m), 2.46 (4 H, m), 3.30 (2 H, m), 3.54 (1 H, m), 3.98 (1 H, m) and 4.46 (1 H, m); $\delta_C(CDCl_3)$ 26.3 (t), 29.7 (t), 43.6 (t), 49.2 (d), 50.1 (t), 73.9 (d), 81.1 (s) and 174.3 (s); ν_{max}(neat)/cm^{-1} 3432m, 3287m, 3233m, 2960m, 2924m, 2111w, 1686s, 1411m, 1321m, 1261m, 1237m, 1174m, 1134w and 838m; *m/z* (rel. int.) 264 (6), 263 (68), 262 (8), 155 (18), 137 (9), 136 (100), 126 (16), 122 (51), 108 (21), 94 (18), 93 (35), 84 (43), 82 (15), 80 (30), 68 (30), 67 (36), 65 (93), 56 (14) and 55 (47) [Found: *m/z* (HRMS) 262.9799. Calc. for $C_8H_{10}INO$: 262.9809]; $[\alpha]_D^{25}$ +4.2 (*c* 0.0093, CH_2Cl_2).

(S)-N-(2-*Chloroethyl*)-5-*ethynylpyrrolidin*-2-*one* **18**.—A suspension of pulverized KOH (1.1 g, 20 mmol), tetrabutylammonium iodide (TBAI) (1 g, 0.2 equiv.), 1-bromo-2-chloroethane (1.68 cm^3, 20 mmol) and the pyrrolidin-2-one **15** (1.1 g, 10 mmol) in dry THF (30 cm^3) was stirred for 12 h at room temperature. The precipitate was filtered off from the mixture and the filtrate evaporated under reduced pressure to leave an oil. On addition of ether to the oil, the phase transfer catalyst TBAI crystallized and was filtered off. The filtrate was washed with water and brine and then evaporated; the product was isolated by column chromatography (silica/ether). Recovered starting material was treated again with an excess both of ethyl bromoacetate and KOH to give the title compound **18** (1.2 g, 7.1 mmol, 70%); R_F 0.41 (ether); $\delta_H(CDCl_3)$ 2.13 (1 H, m), 2.43 (4 H, m), 3.49 (1 H, m), 3.68 (2 H, m), 3.91 (1 H, m) and 4.52 (1 H, m); $\delta_C(CDCl_3)$ 26.4 (t), 29.5 (t), 41.3 (d), 42.9 (t), 49.9 (t), 73.8 (d), 81.2 (s) and 174.6 (s); ν_{max}(neat)/cm^{-1} 3294m, 3233m, 2930m, 2854m, 2118w, 1691s, 1542w, 1405m, 1360m, 1261m,

1174m, 1034m and 836w; *m/z* (rel. int.) 171 (5), 170 (5), 136 (45), 122 (100), 193 (10), 80 (10), 68 (15), 67 (13), 66 (10), 65 (55), 55 (13), 52 (10), 39 (43), 28 (42) and 27 (45) [Found: *m/z* (HRMS) 262.9799. Calc. for $C_8H_{10}INO$: 262.9809].

(S)-1-*Iodoethyl*-5-(2-*trimethylsilylethynyl*)*pyrrolidin*-2-*one* **19**.—(5S)-1-(2-Chloroethyl)-5-(trimethylsilylethynyl)pyrrolidin-2-one (1.0 g, 4.1 mmol), NaI (2 g, oven-dried *in vacuo*) and anhydrous acetone (20 cm^3) were stirred 12 h under argon and then refluxed for 1 h. The solution was filtered, the solids washed with acetone and the combined filtrate and washings were evaporated under reduced pressure to yield a yellow oil. Ether was added to the oil and the ether solution was then washed with water, saturated aqueous sodium sulfite and brine. Evaporation of the ether solution and column chromatography of the residue gave the title compound **19** (3.2 mmol, 79%); R_F 0.35 (ether); $\delta_H(CDCl_3)$ 0.11 (q), 2.14 (1 H, m), 2.46 (4 H, m), 3.30 (2 H, m), 3.54 (1 H, m), 3.98 (1 H, m) and 4.46 (1 H, m); $\delta_C(CDCl_3)$ 0.62 (q), 26.0 (t), 29.2 (t), 43.3 (t), 48.7 (d), 49.8 (t), 73.7 (d), 81.0 (s) and 174.6 (s); *m/z* (rel. int.) 335 (2), 275 (2), 230 (10), 229 (95), 186 (50), 185 (10), 183 (60), 125 (11), 112 (25), 103 (25), 92 (12), 94 (14), 81 (18), 75 (40), 73 (100), 68 (35) and 55 (25).

(S)-(+)-7-(*Trimethylsilylmethylene*)*hexahydropyrrolizin*-3-*one* **20**.—The pyrrolidin-2-one **19** (0.55 g, 1.6 mmol), tributyltin hydride (0.48 cm^3, 1.8 mmol), and a catalytic amount of AIBN in dry benzene (100 cm^3) were degassed and heated to reflux for 6 h under Ar. The mixture was evaporated under reduced pressure and the residue was subjected to column chromatography (silica/ether) to give the title compound **20** (0.27 g, 1.3 mmol, 80%); R_F 0.35 (ether); $\delta_H(CDCl_3)$ 0.11 (s, 9 H), 1.30 (m, 1 H), 1.80 (m, 1 H), 2.39 (m, 2 H), 2.66 (m, 3 H), 3.10 (m, 1 H), 3.97 (q, 1 H), 4.31 (t, 1 H) and 5.42 (t, 1 H); $\delta_C(CDCl_3)$ −0.6 (q), 27.3 (t), 32.7 (t), 33.9 (t), 41.3 (d), 65.3 (d), 120.0 (d), 158.4 (s) and 176.8 (s); ν_{max}(neat)/cm^{-1} 3357br, 2954s, 2897m, 1694s, 1634m, 1406m, 1336m, 1248m, 1156m, 1110w, 1051w, 866m, 839m, 766m, 692m and 610m; *m/z* (rel. int.) 209 (19), 208 (15), 166 (15), 136 (100), 135 (16), 120 (2), 108 (6), 97 (5), 73 (32), 59 (11) and 55 (6) [Found: *m/z* (HRMS) 209.1222. Calc. for $C_{11}H_{19}NOSi$: 209.1236]; $[\alpha]_D^{25}$ +7.4 (*c* 0.010, EtOH).

(S)-7-*Methylenehexahydropyrrolizin*-3-*one* **21**.—To a stirred solution of the vinylsilane **20** (0.036 g, 0.17 mmol) in 2% aqueous acetonitrile (30 cm^3) was added toluene-*p*-sulfonic acid (0.3 g) in one portion. The mixture was stirred at room temperature for 48 h, and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and acetic acid (0.010 cm^3, 0.18 mmol), triethylamine (0.025 cm^3, 0.18 mmol) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (5 mg) were added in that order. The reaction mixture was stirred for 3 h and then concentrated under reduced pressure. The residue was purified by column chromatography (silica/ether) to give the title compound **21** (0.019 g, 0.14 mmol, 82%);[11,32] $\delta_H(CDCl_3)$ 1.30–3.50 (m, 7 H), 3.78 (td, 1 H), 4.17 (br t, 1 H) and 4.72–4.98 (m, 2 H); $\delta_C(CDCl_3)$ 27.3 (t), 32.7 (t), 33.9 (t), 41.3 (d) and 65.3 (d); ν_{max}(neat)/cm^{-1} 1700; *m/z* (rel. int.) 137 (24) and 83 (100).

(−)-*Isoretronecanol* **22**.—To a stirred solution of the hexahydropyrrolizinone **21** (0.055 g, 0.44 mmol) in dry THF (10 cm^3) cooled with an ice-bath was added borane•THF (1 mol dm^{-3}; 1 cm^3) in one portion. The mixture was stirred at ambient temperature overnight after which the solvents were evaporated and the oil was heated to reflux in ethanol for 6 h. Work-up with H_2O_2 in aqueous sodium hydroxide was followed by concentration of the solution under reduced pressure to give **22** 0.039 g (0.039 g, 0.28 mmol, 63%); $\delta_H(CDCl_3)$ 1.03–2.77 (m, 2 H), 2.77–3.27 (m, 2 H), 3.27–3.85 (d, 3 H) and 4.33 (br s, 1 H); $\delta_C(CDCl_3)$ 27.3 (t), 32.7 (t), 33.9 (t), 41.3 (d), 65.3 (d); ν_{max}(neat)/cm^{-1} 3360br; *m/z* (rel. int.) 141 (24), 140 (12), 124 (20) and 83 (100); $[\alpha]_D^{23}$ −75 (*c* 0.045, EtOH) {lit.,[2b] $[\alpha]_D^{18}$ −70.9 (*c* 2, EtOH)}.

(−)-1-(*But*-1-*enyl*)-5-*ethoxycarbonylpyrrolidin*-2-*one*.—Ethyl pyroglutamate **2** (10.0 g, 63.7 mmol), freshly distilled butyraldehyde (11.2 cm^3, 127.0 mmol) and phosphorus pentoxide (9.0 g, 64.0 mmol) were refluxed in dry toluene (200 cm^3). The solution changed from a pale yellow to a dark orange colour and the phosphorus pentoxide changed from a sticky white powder to a thick, bubbling, floating dark mass. The toluene was decanted and washed with aqueous hydrogen carbonate. The remaining semi-solid was dissolved in water and the solution neutralized and extracted with ether. The combined organic layers were evaporated to give a dark orange coloured oil which was further purified by removal of the excess of butyraldehyde by high vacuum rotovap. The crude product was purified by Kugelrohr distillation (155–160 °C, 3 mmHg) to give the title compound (6.05 g, 28.7 mmol, 45%); $\delta_H(CDCl_3)$ 1.21 (3 H, t), 2.25 (4 H, m), 4.21 (1 H, m), 4.80 (2 H, q) and 6.7 (1 H, br); $\delta_C(CDCl_3)$ 14.4 (q), 22.0 (t), 29.5 (t), 56.0 (d), 61.6 (t), 152.0 (s) and 180.0 (s); ν_{max}(neat)/cm^{-1} 3230br, 1740s, 1700s, 1200m, 1100m, 1040m and 740br; *m/z* (rel. int.) 211 (3), 196 (3), 183 (1), 168 (2), 139 (9), 138 (100), 122 (1), 100 (8), 95 (3), 94 (4), 84 (6), 80 (3), 70 (4), 68 (5), 67 (4), 55 (9), 54 (5) and 51 (1) [Found: *m/z* (HRMS) 211.1209 (±0.9 mmu). Calc. for $C_{11}H_{17}NO_3$ 211.1218]; $[\alpha]_D^{25}$ −16.4 (*c* 0.0521, CH_2Cl_2).

(S)-(+)-1-(*Ethoxycarbonylmethyl*)-5-*vinylpyrrolidin*-2-*one*.—A suspension of pulverized KOH (1.0 g, 18 mmol) and tetrabutylammonium iodide (0.84 g, 0.20 equiv.) in dry THF (50 cm^3) was stirred mechanically in a 3-neck round-bottom flask. The flask was submerged in a sonic bath (Bransonic 220) whilst a solution of ethyl bromoacetate (2.51 cm^3, 22.6 mmol) and the pyrrolidinone **8** (1.25 g, 11.3 mmol) in dry THF (50 cm^3) was added to it over 1 h *via* a syringe at room temperature with sonication. After the addition, the reaction mixture was stirred for 12 h with sonication at room temperature. The precipitate was filtered off and the filtrate evaporated under reduced pressure to leave an oil. On addition of ether to the oil the phase catalyst crystallized and was filtered off. The filtrate was washed with water and brine and then evaporated. Column chromatography (silica/ether) afforded the product; only *ca.* 50% of the vinylpyrrolidinone appeared to have reacted. Recovered **8** was treated again with an excess of both ethyl bromoacetate and KOH under similar conditions. Work-up yielded the title compound in 73% yield (1.63 g, 8.25 mmol); R_F 0.48 (ether); $\delta_H(CDCl_3)$ 1.28 (t, 3 H), 1.85 (m, 1 H), 2.42 (m, 3 H), 3.65 (d, 2 H), 4.2 (q, 3 H), 5.26 (dd, 2 H) and 5.66 (m, 1 H); $\delta_C(CDCl_3)$ 14.1 (q), 25.7 (t), 29.8 (t), 42.0 (t), 61.7 (d), 61.9 (t), 119.1 (t), 137.4 (d), 168.8 (s) and 175.6 (s); ν_{max}(neat)/cm^{-1} 3477, 3082, 2983, 2938, 1749, 1696, 1421, 1264, 1202, 1025, 934, 731, 566 and 510; *m/z* (rel. int.) 197 (25), 168 (3), 151 (15), 124 (100), 110 (25), 96 (22), 95 (20), 81 (15), 68 (15), 67 (40) and 44 (48) [Found: *m/z* (HRMS) 197.1050. Calc. for $C_{10}H_{15}NO_3$: 197.1052]; $[\alpha]_D^{25}$ +14 (*c* 0.096, CH_2Cl_2).

(S)-(−)-1-(2-*Hydroxyethyl*)-5-*vinylpyrrolidin*-2-*one Methanesulfonate*.—Triethylamine (0.45 cm^3, 3.2 mmol) in CH_2Cl_2 (15 cm^3) was added dropwise *via* a syringe over 1 h to a stirred solution of the pyrrolidin-2-one **9** (0.47 g, 3.0 mmol) and methanesulfonyl chloride (0.24 cm^3, 3.1 mmol) in CH_2Cl_2 (100 cm^3) cooled to −78 °C. The solution was allowed to warm to ambient temperature and stirred for 3 h. Extractive work-up and column chromatography (silica/ether) gave the title compound (0.36 g, 1.5 mmol, 51%); R_F 0.08 (ether);

$\delta_H(CDCl_3)$ 1.82 (m, 1 H), 2.41 (m, 3 H), 3.05 (s, 3 H), 3.27 (m, 1 H), 3.80 (m, 1 H), 4.21 (m, 3H), 5.27 (m, 2H) and 5.67 (m, 1H); $\delta_C(CDCl_3)$ 25.6 (t), 29.7 (t), 37.6 (t), 40.1 (q), 62.3 (d), 66.7 (t), 119.1 (t), 137.0 (d) and 176.0 (s); ν_{max}(neat)/cm^{-1} 3415, 3082, s, 2930, 1678, 1420, 1352, 1264, 1170, 973 and 798; *m/z* (rel. int.) 233 (10), 206 (2), 178 (4), 154 (79), 138 (21), 137 (9), 136 (24), 126 (8), 125 (9), 124 (100), 110 (10), 96 (19), 95 (26), 94 (7), 82 (23), 81 (21), 79 (26), 68 (15), 67 (58), 60 (8), 66 (11), 65 (20), 42 (25) and 41 (51) [Found: *m/z* (HRMS) 233.0716. Calc. for $C_9H_{15}NO_4S$: 233.0722]; $[\alpha]_D^{25}$ −26.5 (*c* 0.096, CH_2Cl_2).

(S)-(−)-1-(*Ethoxycarbonylmethyl*)-5-*ethynylpyrrolidin*-2-*one*.—A suspension of pulverized KOH (0.73 g, 13 mmol) and tetrabutylammonium iodide (TBAI) (0.7 g, 0.2 equiv.) in dry THF (20 cm^3) was stirred mechanically in a 3-neck round-bottom flask. The flask was submerged in a sonic bath (Bransonic 220) whilst a solution of ethyl bromoacetate (1.9 cm^3, 18 mmol) and the pyrrolidin-2-one **15** (0.95 g, 8.7 mmol) in dry THF (20 cm^3) were added to it over 1 h *via* a syringe, at room temperature with sonication. After the addition, the reaction mixture was stirred for 12 h with sonication at room temperature. The precipitate was filtered off and the filtrate was evaporated under reduced pressure to leave an oil. On addition of ether to the oil the phase catalyst TBAI crystallized and was filtered off. The filtrate was washed with water and brine and evaporated and the residue was subjected to column chromatography (silica/ether) to give the title compound (5.5 mmol, 63%); R_F 0.40 (ether); $\delta_H(CDCl_3)$ 1.28 (3 H, m), 2.21 (1 H,m), 2.49 (3 H, m), 3.79 (1 H, m), 4.22 (3 H, m) and 4.50 (2 H, m); $\delta_C(CDCl_3)$ 14.2 (q), 26.2 (t), 29.4 (t), 42.0 (t), 49.3 (d), 61.4 (t), 74.2 (d), 80.9 (s), 168.7 (s) and 174.6 (s); ν_{max}(neat)/cm^{-1} 3450, 3250, 2990, 2910, 2100, 1745, 1687, 1400, 1343, 1250, 1190, 1095, 1011 and 660; *m/z* (rel. int.) 195 (1), 166 (34), 138 (25), 123 (39), 122 (100), 121 (16), 108 (14), 94 (16), 93 (28), 80 (13), 68 (35), 67 (31), 66 (23), 65 (60) and 55 (35); $[\alpha]_D^{25}$ −36.5 (*c* 0.096, CH_2Cl_2).

(S)-(+)-5-*Ethynyl*-1-(2-*hydroxyethyl*)*pyrrolidin*-2-*one Methanesulfonate*.—Triethylamine (0.64 cm^3, 4.6 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise *via* a syringe over 1 h to a stirred solution of the pyrrolidin-2-one **16** (0.60 g, 40 mmol) and methanesulfonyl chloride (0.34 cm^3, 4.3 mmol) in CH_2Cl_2 (100 cm^3) at −78 °C. The solution was allowed to warm to ambient temperature and stirred for 3 h. Extractive work-up and column chromatography (silica/ether) of the residue gave the title compound (0.66 g, 2.8 mmol, 71%) as a yellow oil: R_F 0.24 (ether); $\delta_C(CDCl_3)$ 2.14 (2 H, m), 2.45 (3 H, m), 3.05 (3 H, m), 3.50 (1 H, m), 3.97 (1 H, m) and 4.39 (3 H, m); $\delta_C(CDCl_3)$ 26.3 (t), 29.5 (t), 37.7 (t), 40.4 (t), 49.8 (d), 66.5 (t), 74.0 (d), 81.1 (s) and 174.8 (s); ν_{max}(neat)/cm^{-1} 3430, 3279, 3021, 2937, 2111, 1683, 1417, 1350, 1173, 911, 907 and 803; *m/z* (rel. int.) 153 (9), 152 (98), 134 (23), 124 (24), 122 (100), 106 (21), 94 (14), 93 (27), 56 (8) and 55 (35); $[\alpha]_D^{25}$ +23 (*c* 0.056, CH_2Cl_2).

(S)-1-(2-*Chloroethyl*)-5-(2-*trimethylsilylethynyl*)*pyrrolidin*-2-*one*.—To a solution of the pyrrolidin-2-one **18** (1.15 g, 6.65 mmol) in dry tetrahydrofuran (250 cm^3) at −78 °C was added butyllithium in hexane (1.4 mol dm^{-3}; 5 cm^3) over 45 min. The mixture was stirred at −78 °C for an additional 30 min after which trimethylsilyl chloride (0.93 cm^3, 7.3 mmol) was added to it dropwise over 30 min. The mixture was allowed to warm to room temperature and then stirred overnight. After this the mixture was cooled to −5 °C and 5% aqueous hydrochloric acid was added to it. The organic phase was extracted with ether (× 3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (1.38 g, 5.65 mmol, 85%); R_F 0.41 (ether); $\delta_H(CDCl_3)$ 0.10 (s, 9 H), 2.10 (1 H, m), 2.41 (4 H, m), 3.34 (1 H, m), 3.72 (2 H, m), 3.92 (1 H, m) and 4.55 (1 H, m); $\delta_C(CDCl_3)$ − 0.5 (q), 26.9 (t), 30.1 (t), 41.0 (d), 43.2 (t), 48.7 (t), 73.5 (d), 81.4 (s), and 174.5 (s); *m/z* (rel. int.) 243 (4), 244 (3), 228 (5), 208 (60), 194 (64), 167 (5), 150 (9), 134 (36), 124 (7), 109 (9), 96 (12), 93 (40), 75 (45), 73 (100), 68 (50), 55 (35) and 43 (40) [Found: *m/z* (HRMS) 243.0841 (± 1.2 mmu). Calc. for $C_{11}H_{18}ClNOSi$ 243.0846].

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