N-Alkenyl Nitrone Dipolar Cycloaddition Routes to Piperidines and Indolizidines. Part 7.[1] Hydroxylamine–Alkyne Cyclisations. Formation of Cyclic Nitrones and Application to the Synthesis of the Proposed Structure for (±)-Acacialactam

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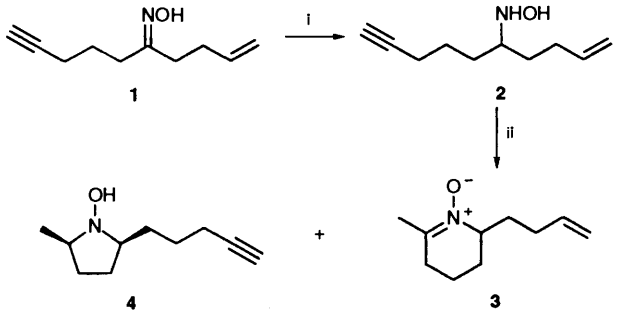
The cyclisation of the alkynylhydroxylamines **2**, **13**, **14**, **19**, **27**, **34**, **39**, **46** and **47** to give five-, six- and seven-membered cyclic nitrones is described. A concerted intramolecular ene-like pathway is proposed for the addition of the N–O–H group across the triple bond. Using the nitrone **48** as the starting material, the seven-membered lactam structure **49** proposed for the natural product acacialactam was prepared and was found to be incorrect.

In recent years, there has been considerable interest in the cyclisations of unsaturated hydroxylamines and oximes. House and co-workers were the first group to study the formation of *N*-hydroxypyrrolidines by a proposed 5-*exo*-*trig* radical cyclisation of pent-4-enylhydroxylamines.[2] This reaction was subsequently studied and exploited by a variety of research groups,[3–9] and the reaction for *N*-alkyl-*N*-pent-4-enylhydroxylamines was recently classified by Ciganek as a reverse Cope elimination.[10] Closely related cyclisations of oximes onto allenes,[11] alkenes[12] and alkynes[13,14] have been reported by a number of other investigators.

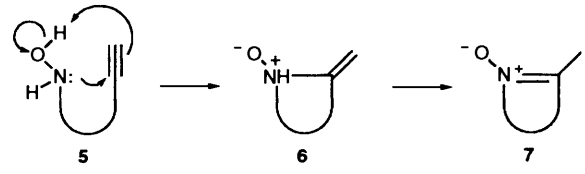
During our synthetic studies on various Dendrobatid indolizidines,[14] we observed that hex-5-ynylhydroxylamine derivative **2**, readily prepared from the oxime **1**, cyclised to the tetrahydropyridine *N*-oxide **3** at room temperature (Scheme 1).



Scheme 1 *Reagents and conditions:* i, $NaCNBH_3$ pH 3–4; ii, 20 °C, 1 h [67% (**3**) and 10% (**4**)]

This cyclisation seemed to have much in common with the other cyclisations discussed above and we therefore decided to investigate its mechanism, the scope with respect to ring size, and the influence of substituents. In this paper, we report the results of these studies and the application of the seven-membered nitrone forming reaction to the synthesis of the proposed seven-membered lactam structure of the biologically interesting natural product (+)-acacialactam. During the course of our studies, Ciganek[10] showed that the reverse Cope elimination reaction of *N*-alkyl-*N*-pent-4-enylhydroxylamines followed a concerted pathway and recently Oppolzer[8b] observed a similar result for the unsubstituted pent-4-enylhydroxylamines.

All our studies are consistent with the proposal that the hydroxylamine–alkyne cyclisation follows the path shown in



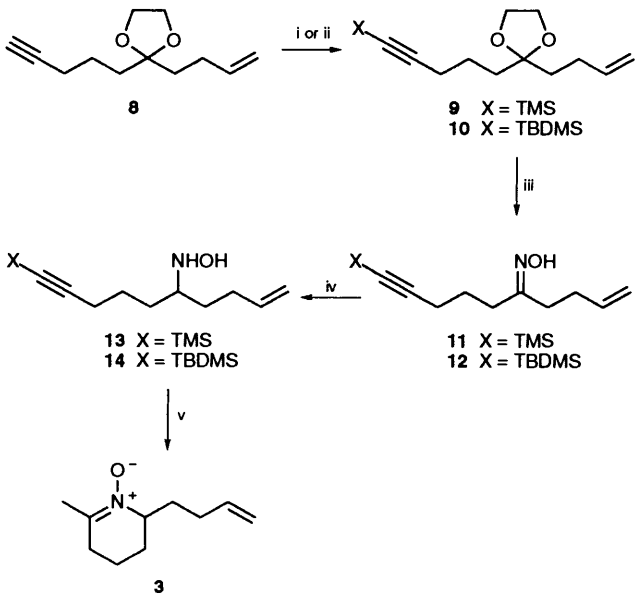
Scheme 2

Scheme 2.[15] After the initial ene-like cyclisation of the hydroxylamine **5** to give an *N*-oxide **6**, proton transfer and tautomerisation lead to a nitrone **7**. The first step in the analogous alkene–oxime cyclisation has been designated by Grigg as a 1,3-azaprotio transfer reaction.[12e]

The cyclisation of the hex-5-ynylhydroxylamine **2** afforded the nitrone **3** (a 6-*exo*-*dig* cyclisation product)[14] and a small quantity of the *cis*-*N*-hydroxypyrrolidine **4**, resulting from the competing 5-*exo*-*trig* cyclisation of the hydroxylamine group onto the double bond. The *cis*-isomer **4** was the only isomer isolated. There is a delicate balance between the competing alternative 5-*exo*-*trig* and the 6-*exo*-*dig* modes of cyclisation for this compound, with the latter apparently being favoured. It is unclear why the *trans*-pyrrolidine was not found, as studies with the closely related compound **19** (Scheme 5) showed that the *trans*-product predominated in the 5-*exo*-*trig* cyclisation.

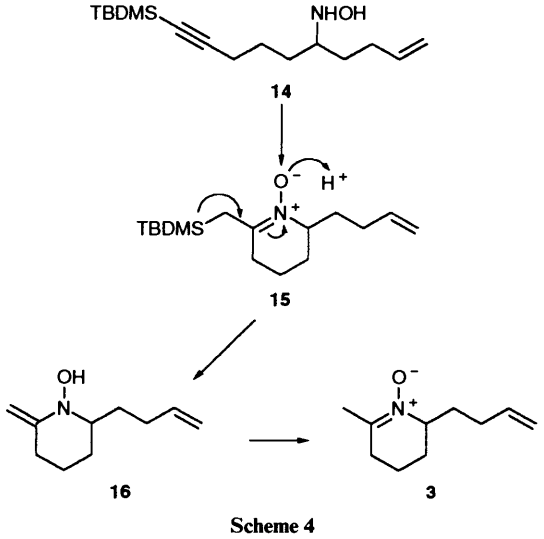
A radical pathway[2] for the hydroxylamine–alkyne cyclisation was discounted by a careful study of the conversion of the relatively unstable hydroxylamine **2** [R_f 0.60, ethyl acetate–methanol (9:1), kieselgel thin layer chromatography] into the nitrone **3**. The reaction proceeded in 67% yield and was unaffected both by the exclusion of oxygen (freeze–thaw degassing) and the addition of the radical scavenger galvinoxyl.[16] These results parallel those of Black[3] and support the conclusion that a radical pathway can be ruled out.

Cyclisations involving terminal alkynes necessarily produce only the methyl-substituted nitrone. The reaction would be considerably more versatile if a variety of substituted alkynes could be produced. We therefore studied the cyclisation of the hydroxylamines **13** and **14** in the expectation that the terminal silyl substituents would provide functionality in the methyl side-chain of the nitrone product (Scheme 3). These were prepared by silylation of the terminal alkyne **8**[17] followed by conversion of the respective 1,3-dioxolanes **9** and **10** into the corresponding oximes **11** and **12**; these were then reduced to the hydroxylamines **13** and **14**. Both these silyl alkynes afforded the nitrone **3** in which the silyl group had been lost.



Scheme 3 *Reagents and conditions:* i, BuLi, Me_3SiCl (99%); ii, BuLi, Bu^tMe_2SiCl (54%); iii, NH_2OH·HCl, HCl [89% (**11**) and 98% (**12**)]; iv, $NaCNBH_3$ pH 3–4; v, 20 °C 1 h [69% (from **11**) and 62% (from **12**)]

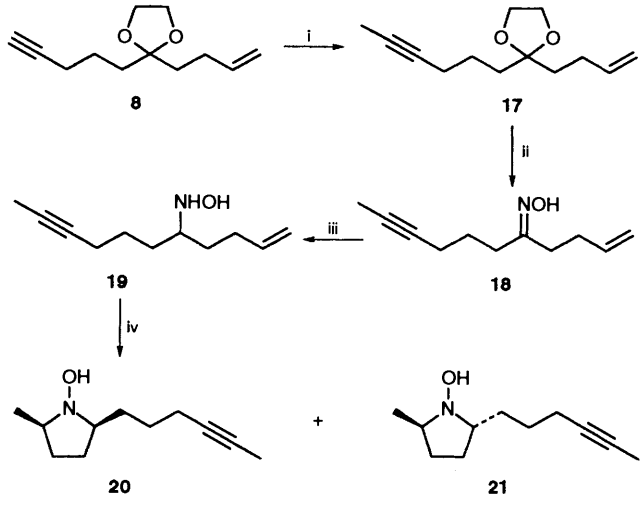
The silyl group could have been lost at various stages such as in the reduction reaction or work-up, rather than during the cyclisation. That desilylation was occurring in the cyclisation rather than during the reduction of the oxime was established by ^1H NMR spectroscopy of the very unstable TBDMS-alkynylhydroxylamine **14** (half-life *ca.* 15 min at 20 °C) in $CDCl_3$. The signal at δ 2.91–2.78 (1 H, m) due to the methine proton on the carbon bearing the hydroxylamine substituent in compound **14** disappeared over a period of 90 min, while the corresponding proton in the spectrum of the nitrone **3** appeared at δ 3.70–3.60 (1 H, m) and the signal due to the Me_2Si protons [δ(250 MHz; $CDCl_3$) 0.07 (6 H, s)] became complex, due to the production of various unidentified desilylation products. In addition, transient signals assigned to the silyl nitrone **15** (Scheme 4) at δ 1.72 (broad singlet, CH_2Si)



Scheme 4

and δ 0.16 (singlet, Me_2Si) grew and decayed together. The mechanism shown rationalises these observations. The loss of silicon is readily explained once it is recognised as being effectively an allylsilane owing to the presence of the neighbouring positively charged nitrogen centre. Following desilylation, tautomerisation of the enehydroxylamine **16** leads to the nitrone **3**.

We then decided to explore the cyclisation of *C*-substituted alkynes as an approach to *C*-substituted cyclic nitrones. To determine whether this was possible, the cyclisations of methylated alkynes **19** (Scheme 5) and **27** (Scheme 6) were attempted.



Scheme 5 *Reagents and conditions:* i, BuLi, tetramethylethylenediamine (TMEDA), MeI (92%); ii, NH_2OH·HCl, HCl (79%); iii, $NaCNBH_3$, pH 3–4; iv, 20 °C [yield of (**20**): 25%; yield of (**21**): 58%]

The hydroxylamine **19** was prepared by the usual route involving methylation of the alkyne **8**, conversion of the dioxolane **17** into the oxime **18** and finally reduction. The hydroxylamine **19** underwent a remarkable cyclisation onto the double bond to give the pyrrolidines **20** and **21**. The more polar product **21** was assigned as the *trans*-isomer on the basis of a ^1H NMR experiment in which a nuclear Overhauser enhancement (NOE) was detected between 2-H adjacent to nitrogen [δ_H(250 MHz; $CDCl_3$) 3.09–3.04 (1 H, m)] and the 5-methyl group (δ 1.94, 3 H, d, *J* 6.7) (Fig. 1). The chemical shifts of the 2-H and 5-H protons in the less polar isomer **20** [δ_H(250 MHz; $CDCl_3$) 2.62 (2 H, m)] were too close for NOE and decoupling studies. In addition, the carbons C-2 and C-5 [δ_C(100 MHz; $CDCl_3$) 65.8 (br d) and 61.5 (br d)] and the respective adjacent carbons, CH_2 [δ 32 (br)] and Me [δ 16 (br)], in the ^{13}C NMR spectrum of *trans*-compound **21** gave broad signals. This may be accounted for by considering the inversion of the nitrogen lone pair (Fig. 2). Both conformers of the *trans*-compound **21** have an alkyl group on the same face of the five-membered ring as the hydroxyl group and are therefore likely to have similar energies. Slow interconversion of these conformers would cause broadening of the signals of the carbons near the nitrogen. The two conformers of the *cis*-pyrrolidine **20**, which does not display any line broadening in the ^{13}C NMR spectrum would have different energies, and this compound would have a strong preference for the conformer in which the hydroxyl group is on the opposite face of the five-membered ring to the two alkyl groups.

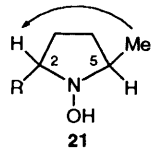


Fig. 1

The cyclisation shown in Scheme 5 arose from the presence of a double bond as a competing site for cyclisation of the

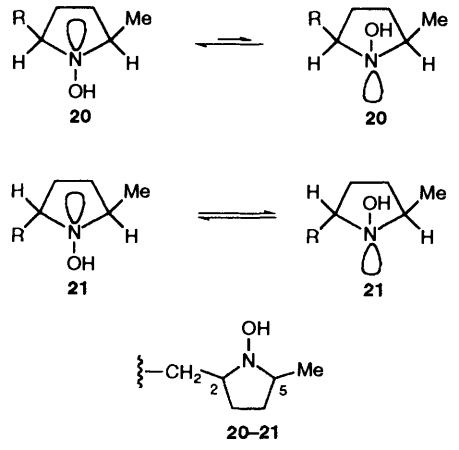


Fig. 2

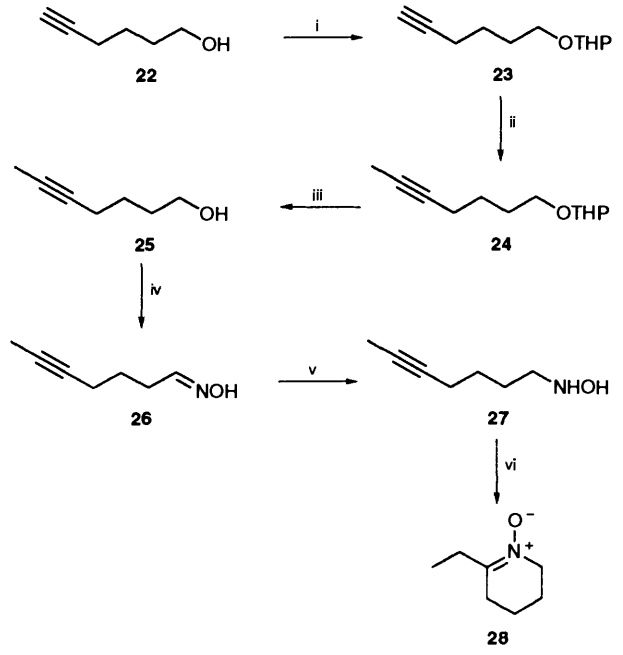
Table 1 Typical chemical shifts in substituted alkynes $R-C_1\equiv C_2-X$ (R = primary alkyl)

X	δ C-1 (ppm)	δ C-2 (ppm)
H	80–85	60–70
R'_3Si	100–110	80–90
Me	75–80	75–80

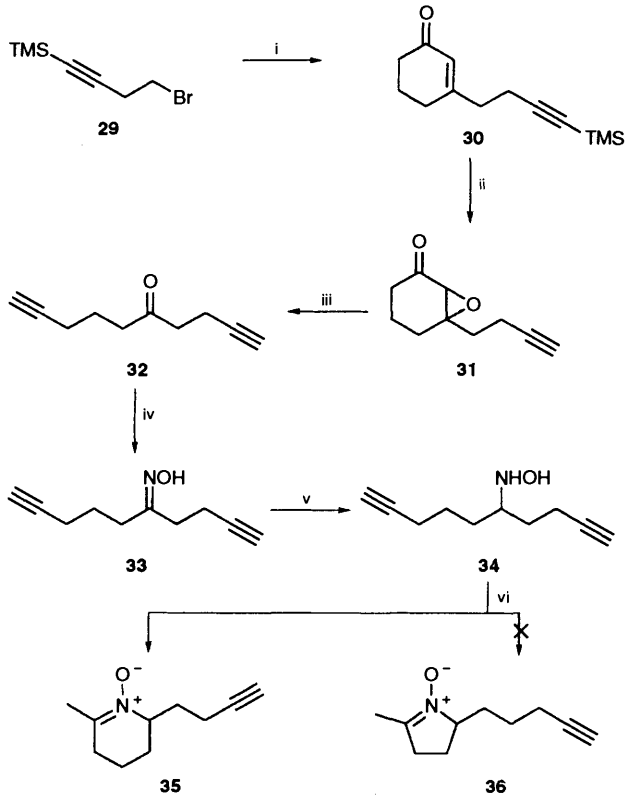
hydroxylamine **19**. In order to remove this competing pathway, the hydroxylamine **27**, lacking the double bond, was synthesised by methylation of the tetrahydropyranyl (THP) ether **23** derived from hex-5-yn-1-ol **22**. Removal of the THP group, followed by oxidation of the alcohol **25** to the aldehyde and treatment with hydroxylamine hydrochloride, gave the oxime **26**. Reduction afforded the corresponding hydroxylamine **27** which was much less reactive than unsubstituted or silyl substituted alk-5-ynylhydroxylamines. However, when heated in refluxing toluene, the hydroxylamine **27** gave a high yield of the nitrone **28**.

Black [3] and Ciganek,[10] in their studies of the hydroxylamine–alkene cyclisation, observed that 1,2-substituted alkenes were less reactive than terminal alkenes. There are two factors which may lower the reactivity of a methyl-substituted alkyne relative to a terminal alkyne. Firstly, a methyl group is bulkier than hydrogen. However, it is noted that silyl substituents on alkynes do not apparently decrease reactivity of the alkyne, despite the increased bulk of the silyl group. Secondly, the electronic effect of the substituent may be important. The effect on the ^{13}C NMR chemical shifts of the triply bonded carbons of these substituents is shown in Table 1. Carbon chemical shifts correlate with the electron density and hence show the effect of substituents on the HOMO coefficients of the alkyne. The lack of polarisation of the triple bond when both substituents are alkyl groups contrasts with the situation where a hydrogen or silyl substituent is present, when the greatest electron density is on C-2, which also has the lower chemical shift.

As the 6-*exo-dig* cyclisation was favoured over the alternative 5-*exo-trig* cyclisation by a factor of about 7, as estimated from the ratios of products obtained in the cyclisation of hydroxylamine **2** (Scheme 1), and also as the 5-*exo-trig* hydroxylamine–alkene cyclisations are favoured over the 6-*exo-trig* cyclisations,[10] it seemed reasonable that the relative rates of the 6-*exo-dig* and the 5-*exo-dig* cyclisations might be measured directly by a competition experiment similar to the cyclisation of hydroxylamine **2** (Scheme 1). The hydroxylamine **34** was synthesised for this purpose using an Eschenmoser fragmentation [18,19] of the epoxycyclohexanone **31** to form the ketone **32**, which was converted into the oxime **33** (Scheme 7). Compound



Scheme 6 *Reagents and conditions:* i, Dihydropyran, 4-methylbenzenesulfonic acid (TsOH) (100%); ii, BuLi, TMEDA, MeI (92%); iii, MeOH, TsOH (98%); iv, PCC followed by NH_2OH·HCl, Py (63%); v, $NaCNBH_3$ pH 3–4; vi, toluene, reflux 2 h (94%)



Scheme 7 *Reagents and conditions:* i, Mg, 3-ethoxycyclohex-2-enone-(68%); ii, NaOH, H_2O_2 (71%); iii, methylbenzenesulfonohydrazide ($TsNHNH_2$), AcOH (49%); iv, NH_2OH·HCl, Py (71%); v, $NaCNBH_3$ pH 3–4; vi, 20 °C 1 h (92%)

31 was prepared by epoxidation of the desilylated cyclohexenone **30**, itself prepared by standard addition of the Grignard derived from the bromide **29** to 3-ethoxycyclohex-2-enone.

The hydroxylamine **34** cyclised rapidly to a single product, shown by a 400 MHz COSY spectrum to be the six-membered

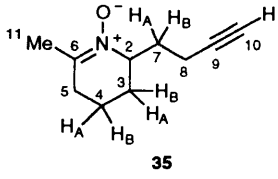


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Fig. 3

Table 2 Assignment of the 400 MHz ^{1}H NMR spectrum of nitrone **35** in C_6D_6 (Fig. 3)

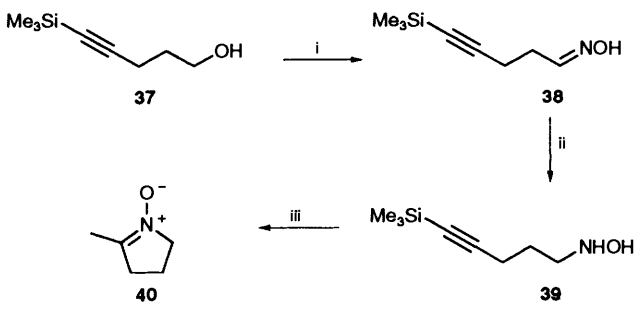
Signal δ (ppm)	Assignment	Coupled protons
3.67–3.58 (1 H, m)	2-H	7-H_A, 7-H_B, 3-H_A, 3-H_B, 11-H_3
2.49–2.36 (1 H, m)	7-H_A	2-H, 7-H_B and 8-H_2
2.35–2.10	8-H_2	7-H_A, 7-H_B and 10-H
1.88 (3 H, br s)	11-H_3	2-H and 5-H_2
1.84 (1 H, t, *J* 2.5)	10-H	8-H_2
1.64–1.55 (3 H, m)	5-H_2 and 7-H_B	2-H, 7-H_A, 8-H_2, 11-H_3, 4-H_A and 4-H_B
1.36–1.25 (1 H, m)	3-H_A	2-H, 3-H_B, 4-H_A and 4-H_B
1.24–1.13 (1 H, m)	3-H_B	2-H, 3-H_A, 4-H_A and 4-H_B
1.06–0.96 (1 H, m)	4-H_A	5-H_2, 3-H_A, 3-H_B and 4-H_B
0.94–0.84 (1 H, m)	4-H_B	5-H_2, 3-H_A, 3-H_B and 4-H_A

nitrone **35**. The signal of the proton 2-H [δ_H(400 MHz; C_6D_6) 3.67–3.58 (1 H, m)] of the nitrone **35** (Fig. 3) was readily assigned on the basis of its chemical shift. The resonances of the methyl group 11-H_3 [δ_H(400 MHz; C_6D_6) 1.88 (3 H, br s)] and the acetylenic proton 10-H [δ_H(400 MHz; C_6D_6) 1.84 (1 H, t, *J* 2.5)] were also readily assigned. Protons of the intervening methylene groups were assigned by following the couplings away from the proton 2-H until the termini of the spin system, 11-H_3 and 10-H were reached. In addition to three-bond couplings, long-range couplings between the protons 2-H and 11-H_3, between the protons 5-H_2 and 11-H_3 and between the protons 8-H_2 and 10-H are present. The full assignment of the spectrum is given in Table 2.

This assignment was supported by a consideration of mass spectra. The EI mass spectrum of the nitrone **35** resembled that of the nitrone **3** (Scheme 1).[14] The ion at *m/z* 113 corresponds to the loss of the four-carbon side-chain from the nitrone **35**. The loss of a five-carbon side chain from the alternative five-membered cyclic nitrone structure **36** would have given an ion at *m/z* 100. No such fragmentation was observed in the mass spectrum of the nitrone **35**.

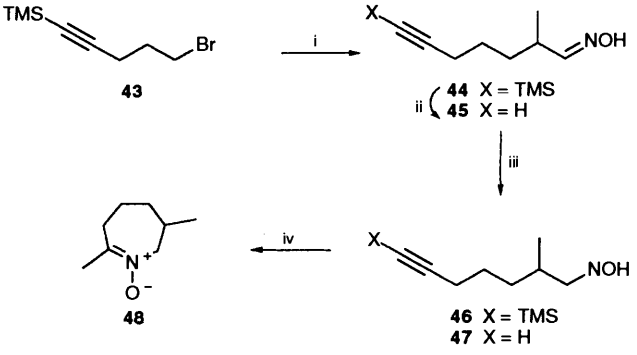
To show that five-membered rings could be produced in the absence of competing reactions, the hydroxylamine **39** was synthesised (Scheme 8). The presence of the silyl group was considered unimportant, as in the six-membered series, silyl groups on the alkyne having no substantial effect on the reactivity in cyclisation (*cf.* Scheme 3). 5-(Trimethylsilyl)pent-4-yn-1-ol **37** was oxidised to the aldehyde, which was converted *via* the oxime **38** into the hydroxylamine **39**. This cyclised with difficulty to give the nitrone **40**.

The high kinetic preference for 6-*exo* cyclisation over 5-*exo* cyclisation is contrary to the trend for cyclisations of carbon centred radicals,[20] which exhibit a kinetic preference for the 5-*exo* over the 6-*exo* cyclisation mode. This is strong evidence against a free-radical chain mechanism. This trend may, however, be readily explained by consideration of the transition states for the concerted mechanism (Fig. 4). The transition state for six-membered ring closure **41** is clearly less strained than the transition state for five-membered ring closure **42**. For the hydroxylamine–alkene cyclisation,[10] five-membered ring closure is kinetically favoured. Accommodating a triple bond in the five-membered transition state **42** is clearly more difficult than accommodating a double bond. When the triple bond can be accommodated, however, as in the cyclisation of



Scheme 8 *Reagents and conditions:* i, PCC followed by NH_2OH·HCl, Py (39%); ii, $NaCNBH_3$, pH 3–4; iii, benzene, reflux 16 h (43%)

Fig. 4



Scheme 9 *Reagents and conditions:* i, $EtCH{=}NNMe_2$, LDA followed by NH_2OH·HCl, pyridine (69%); ii, $Bu_4N^+F^-$ (95%); iii, $NaCNBH_3$, pH 3–4; iv, see Table 3

hydroxylamine **2** (Scheme 1) in forming a six-membered ring, the triple bond has a higher intrinsic reactivity than a double bond.

Synthesis of Seven-membered Rings.—The cyclisations of the hydroxylamines **46** and **47** (Scheme 9) were attempted. These compounds were efficiently prepared using a Corey–Enders alkylation[21] of a hydrazone anion as the key step. Propionaldehyde *N,N*-dimethylhydrazone was lithiated and the anion was alkylated with the bromide **43**. The alkylated hydrazone product was converted *in situ* into the oxime **44** which was reduced or desilylated and reduced to the corresponding hydroxylamines **46** and **47**. The cyclisation of the silylated alkynylhydroxylamine **46** proceeded at negligible rate at ambient temperature, but rapidly in refluxing toluene. The yield of nitrone **48** was poor and was not improved by use of extended reaction times. The unsubstituted alkyne **47** exhibited similar reactivity to the silylated compound **46**, but the reaction was cleaner and the yield was greater.

The hydroxylamine–alkene cyclisation (*retro*-Cope elimination)[10] and Cope elimination[22] reactions show very strong dependence on the nature of the solvent, the former being accelerated and the latter dramatically retarded in protic solvents. These stabilise the *N*-oxide by hydrogen bond donation, resulting in a change in rate by a factor of 10^6. The effect of using representative non-polar aprotic (benzene and carbon tetrachloride), polar aprotic (acetonitrile) and protic (ethanol) solvents on the formation of the nitrone **48** was investigated. These results are summarised in Table 3. The reactions were

Table 3 Effects of solvent on the cyclisation of the hydroxylamines **46** and **47**

Hydroxylamine	Solvent	b.p. (°C)	Reaction time (h)	Yield (%)
46	Toluene	110	16	50
47	Toluene	110	1	81
47	Benzene	81	18	82
47	CCl_4	77	21	19
47	Acetonitrile	80	9	47
47	Ethanol	78	18	78

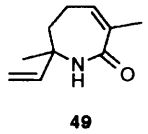


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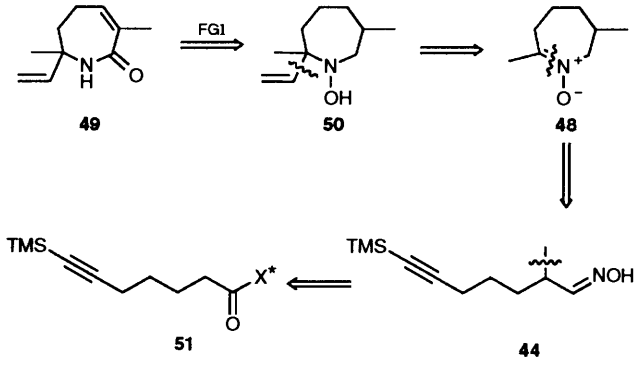
Fig. 5

performed in refluxing solvents with similar boiling points. In all cases, the reaction half-life was similar, about 3 h as determined by TLC. Use of the more reactive solvents, carbon tetrachloride and acetonitrile, led to extensive decomposition after extended periods. This lack of strong solvent dependence differs from the Cope elimination and parallels that in the thermal elimination of nitrones to form oximes and alkenes,[23,24] and analogously, may reflect the relative extents of C–N and C–H bond formation in the transition state.

The nitrone **48** is a suitable starting material for synthesis of the proposed seven-membered lactam structure **49** of the natural product (±)-acacialactam. Seven-membered lactams are rare in nature.[25] Other than the structure (Fig. 5) proposed for acacialactam by Sekine *et al.*,[26] the only known examples are the bengamides, and the related isobengamide. This group of compounds were isolated from an undescribed Fijian sponge of the Jaspidae family.[27] Syntheses of bengamides A[28], B[29] and E[29–31] have been reported. The structure **49** differs from the bengamides in several respects, being an α,β-unsaturated lactam, rather than a saturated one. It is of monoterpenoid derivation, with an unprecedented oxidation level and heteroatom substitution pattern. The compound was isolated from the seeds of *Acacia concinna*, a Thai leguminous tree.[23] Little was known about the biological activity, because of the meagre amounts available, but the seeds had been used for the treatment of skin diseases in Thailand. The supplies of the compound were too small to determine whether it was the active component, but the unusual structure suggested that this was a possibility. The absolute stereochemistry was not known and the determination of this was an additional incentive for synthesis.

A novel approach to the construction of the seven-membered lactam **49** was used (Scheme 10). It was envisaged that the target structure could be produced by functional group interconversion of the hydroxylamine **50**. The hydroxylamine **50** was expected to be available from the addition of a vinyl anion equivalent such as vinylmagnesium bromide to the nitrone **48**. It was anticipated that the existing chiral centre in the nitrone **48** could be used to control the relative stereochemistry at the quaternary centre of the hydroxylamine **50** by directing the approach of the nucleophile to one face of the nitrone **48**. The use of a single enantiomer of the nitrone **48** of known absolute configuration would result in an enantioselective synthesis of the lactam **49** and the assignment of the absolute configuration of the target. Asymmetric methylation[32,33] of a chiral enolate of the hept-6-ynoic acid[34] derivative **51** would lead to the required oxime precursor **44**.

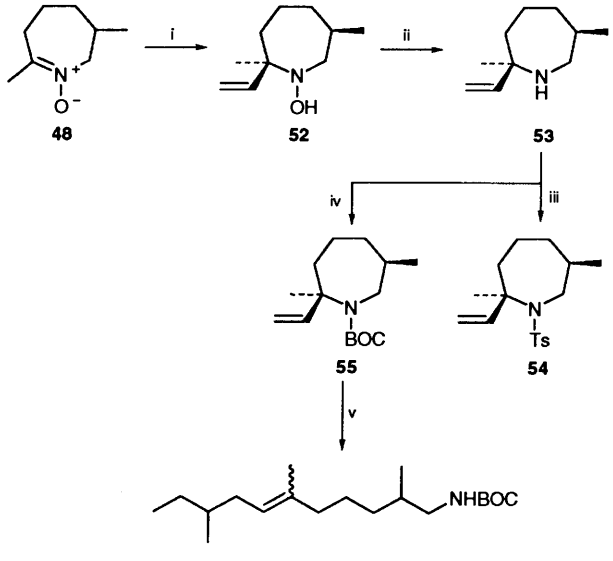
The addition of Grignard reagents to chiral acyclic nitrones has been shown to proceed with moderate to high diastereoselectivity.[35,36] The only example of the addition of a Grignard



Scheme 10

reagent to a chiral cyclic nitrone (five-membered), however, proceeded with low diastereoselectivity.[37]

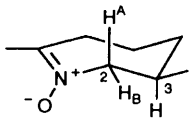
The addition of vinylmagnesium bromide to the nitrone **48** gave a single diastereoisomer of the hydroxylamine **52** (Scheme 11). Reduction of the hydroxylamine **52** to the amine **53**



Scheme 11 *Reagents and conditions:* i, vinylmagnesium bromide −78 °C (81%); ii, $TiCl_3$, H_2O; iii, TsCl, DMAP, Et_3N (52%); iv, di-*tert*-butyldicarbonate (BOC_2O), NaOH (91%); v, *sec*-BuLi, TMEDA (86%)

and protection of the nitrogen with a methylbenzenesulfonyl group gave the crystalline sulfonamide **54**. X-Ray crystal structure determination[38] revealed the molecule **54** to have the (2*R**,6*S**) configuration.

The nitrone **48** was expected to have the chair-like conformation shown in Fig. 6 with a *pseudo*-equatorial methyl group. Support for this conformation of the nitrone **48** was provided by the ^1H NMR spectrum. The protons 2-H_A[δ_H(250 MHz; $CDCl_3$) 4.01 (1 H, dd, *J* 13.4 and 9.3)] and 2-H_B[δ_H(250 MHz, $CDCl_3$) 3.87 (1 H, d, *J* 13.4)] (Fig. 6) were well resolved, but



48

Fig. 6

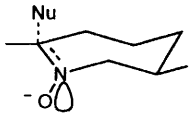


Fig. 7

only one of them was coupled to the adjacent proton 3-H. This suggests that a dihedral angle[39] of *ca.* 90° exists between the protons 2-H_B and 3-H and therefore that the conformation is rigid.

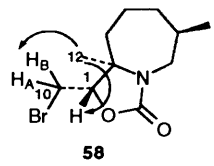
The stereoselectivity of the addition can be rationalised if the nucleophile attacks from the upper face of the nitrone **48**, with the nitrogen lone-pair developing *pseudo*-axially, *trans*-antiperiplanar to the incoming nucleophile in the manner described by Stevens (Fig. 7).[40]

The hydroxylamine **52** was converted into the BOC urethane **55** (Scheme 11). A powerful method of functionalising BOC-protected amines adjacent to nitrogen is by deprotonation with alkyllithiums[41,42] and should be applicable to the BOC-protected amine **55** as a route to the required lactam **49**. However treatment of the urethane **55** with *sec*-butyllithium in the presence of TMEDA (Scheme 11) gave the straight-chain compound **56** by S_N2' addition of a *sec*-butyl group to the double bond in a remarkably clean reaction.

Ruthenium tetroxide is a highly effective reagent for the oxidation of BOC-protected amines to lactams,[43,44] but as this reagent cleaves double bonds, protection of the vinyl group of the BOC-protected amine **55** was necessary. The urethane **55** was treated with bromine (Scheme 12) to give the oxazolidinone **58**. The oxazolidinone **58** has three key features. Firstly, it was expected to be stable to vigorous oxidation conditions. Secondly, the bromine and 1,2-related carbonyloxy substituent were expected to be amenable to reductive elimination, simultaneously revealing the double bond and the lactam nitrogen. Thirdly, the bicyclic compounds in this series were all crystalline solids, a feature which was expected to be of particular assistance in the asymmetric route, where recrystallisation would be the preferred means of purification.

Only one bromolactonisation product, **58** was observed. The stereochemistry was determined by examining the NOEs from the bridgehead methyl group 12-H_3[δ_H(270 MHz; $CDCl_3$) 1.20 (3 H, s)] (Fig. 8). The NOEs observed to bromomethylene protons 10-H_A[δ_H(270 MHz: $CDCl_3$) 3.55 (1 H, dd, *J* 11.0 and 7.1)] and 10-H_B[δ_H(270 MHz; $CDCl_3$) 3.43 (1 H, dd, *J* 11.0 and 6.4)] were about five times stronger than that observed to the methine proton 1-H [δ_H(270 MHz; $CDCl_3$) 4.35 (1 H, t, *J* 6.7)]. This stereoselectivity can be explained if the reactive conformation (Fig. 9) has the double bond eclipsed by the methyl group rather than the bulky ring in a manner analogous to that proposed by Overman[45] for a related cyclisation, in which a *syn* relationship between the bridgehead substituent and the bromomethyl group in the product was also.

When the reaction was repeated on a larger scale, the protocyclisation product **57** was unexpectedly isolated as a side-product, together with the desired product **58**. The side product **57** was probably formed because of the presence of HBr produced during the bromolactonisation. The stereochemistry of the side-product **57** was established by chemical correlation with the bromocyclisation product **58**, which was reduced with



58

Fig. 8

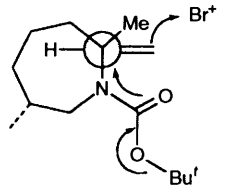
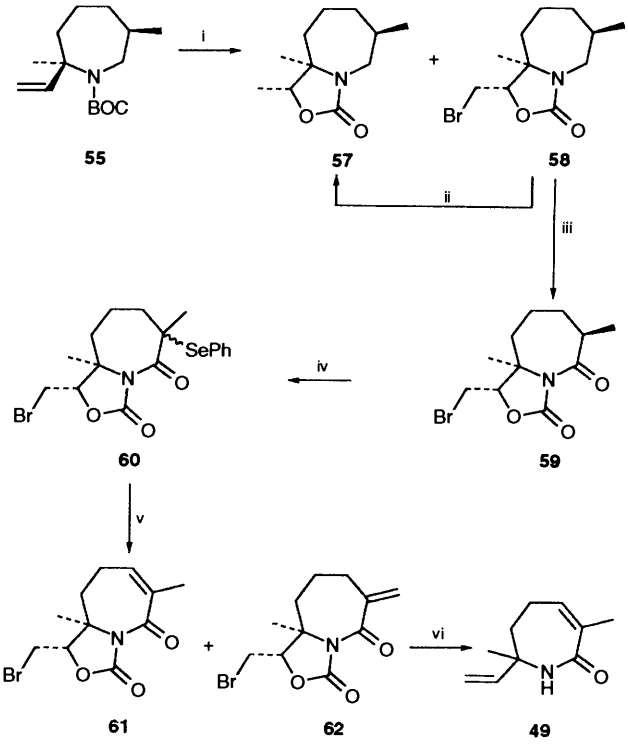


Fig. 9



55 57 58 60 59 61 62 49

Scheme 12 *Reagents and conditions:* i, Br_2 −20 °C (87%); ii, Bu_3SnH, azoisobutyronitrile (AIBN), toluene reflux (98%); iii, $RuCl_3$, $NaIO_4$, H_2O, CCl_4, MeCN (64%); iv, dibutylboron triflate (Bu_2BOTf), 2,6-lutidine, PhSeCl (67%); v, $NaIO_4$ followed by PPh_3 (35%); vi, Zn, NH_4Cl (88%)

tributyltin hydride to the methyl derivative **57**. The oxazolidinone **58** was oxidised to the lactam **59** with ruthenium tetroxide under the Sharpless conditions.[46]

Enolate selenation of the bicyclic oxazolidinone **59**, followed by a selenoxide elimination was used to introduce the endocyclic double bond (Scheme 12). Attempts to enolise the bicyclic oxazolidinone **59** with basic reagents such as lithium diisopropylamide and sodium bis(trimethylsilyl)amide failed. The enolate of the bicyclic compound **59** is strained and hence difficult to form. However, use of the Lewis acidic reagent dibutylboron triflate and the weak base 2,6-lutidine to form the boron enolate, followed by selenation, gave the selenides **60** in a ratio which varied between 1 : 1 and 2 : 1. Selenoxide elimination gave a 1.9–1.3 : 1 mixture of endocyclic **61** and exocyclic **62** unsaturated lactams respectively. Such a ratio was disappointing, but not unexpected in a selenoxide elimination from a rigid bicyclic system.[47] The endocyclic **61** and exocyclic **62** isomers of the unsaturated lactam were inseparable, but treatment of

the mixture of endocyclic **61** and exocyclic **62** alkenes with triphenylphosphine selectively destroyed the exocyclic isomer **62**, presumably by Michael addition to the more electrophilic exocyclic double bond with formation of a phosphonium salt. A ratio of 23 : 1 in favour of the endocyclic isomer **61** was obtained, measured by integrating the signals due to the protons on the endocyclic [δ_H(400 MHz; $CDCl_3$) 6.36 (1 H, t, *J* 4.8)] and exocyclic [δ_H(400 MHz; $CDCl_3$) 5.88 (1 H, d, *J* 1.2) and 5.50 (1 H, br s)] double bonds. A further improvement in ratio to 36 : 1 was obtained by recrystallisation (overall yield 26%). In view of the success and convenience of this procedure, separation of the selenides **60** and independent oxidation of each diastereoisomer, which may have given different ratios of the elimination products **61** and **62**, was not attempted.

Deprotection of the oxazolidinone **62** to the target molecule **49** proceeded under very mild reducing conditions with zinc in ammonium chloride–methanol (88%) (Fig. 10).[48]

Differences between the synthetic lactam (±)-**49** and the natural product[26] occur in the TLC, IR, ^1H and ^{13}C NMR data. In addition, the synthetic material is a solid and the natural product is an oil. Although racemic compounds and single enantiomers may have different melting points, this was the first indication that there was a difference.

Sekine *et al.*[26] found that the natural product was basic, and reported a TLC R_f of 0.35 with the very polar solvent system [ethyl acetate–methanol–ammonia (150 : 9 : 1)]. The synthetic lactam **49** has R_f 0.70 in this medium.

Examination of the original IR and NMR spectra of acacialactam, kindly supplied by Professors Murakoshi and Sekine, revealed a number of interesting features. The IR spectrum (Table 4), in addition to the absorptions reported, had a strong, broad absorption at 3350 cm^{-1} (possible O–H stretch) contrasting with the sharp absorption at 3400 cm^{-1} for the synthetic lactam **49**, and an absorption at 1640 cm^{-1} (possible N–H bending mode).

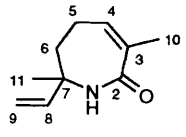
The original ^1H NMR spectrum (Table 5) differed in two important respects from the published data. The NH signal [δ_H(400 MHz; $CDCl_3$) 5.56 (1 H, br)] integrated for two protons, not one, as reported. The signal at δ 1.65 [δ(400 MHz; $CDCl_3$) 1.65, m] integrated for three protons, not two, as reported. These differences suggest that the molecule possesses two extra protons, contains an NH_2 group rather than an NH group, and hence is a straight chain compound, rather than a ring. The other extra proton may well be part of an OH group. This would explain the broad infrared absorption at 3350 cm^{-1} and help to explain the high polarity of the molecule. A straight chain structure is supported by the shape of the two proton 5-H multiplet at δ 2.25, which is symmetrical, in contrast to the two proton 5-H multiplet of the cyclic synthetic material **49** at δ 2.37–2.31, which is non-symmetrical.

The ^{13}C NMR spectrum of the synthetic material **49** differed significantly from that of the natural material, (Table 6). The C-7 signal, in particular, is 16.5 ppm higher (downfield) in the natural product, suggesting that C-7 is attached to oxygen, not nitrogen. The signals arising from the carbon atoms of the conjugated system, however differ by relatively little from those of the natural product. This suggests that the α,β-unsaturated amide functionality is present in both.

The putative molecular ion in the EI mass spectrum of the natural product is small (14%). No CI or FAB spectra were obtained. In the absence of more reliable mass spectral data, the best alternative structure is the structure (*E*)-**63** or (*Z*)-**63** (Fig. 11) which has a molecular weight of 183. This could readily lose water to give a peak at *m/z* 165 in the EI mass spectrum. The only inconsistency of the data with this structure is the chemical shift of the C-11 signal, which would be expected to be larger than δ 12.7. The corresponding carbon signal of the synthetic lactam **49** is at δ 22.5. We concluded that a possible alternative structure for acacialactam is amide **63** (Fig. 11), but did not attempt its synthesis until more information, in particular FAB or CI mass spectra, became available. This conclusion is now supported by an independent synthesis (from linalool) of the amide **63** by Marco and co-workers which clearly establishes the configuration of the trisubstituted double bond as (*E*).[49]

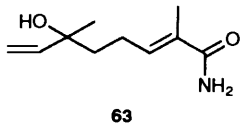
Conclusions

The use of the hydroxylamine alkyne cyclisation was shown to be effective for five-, six- and seven-membered rings, with the order of reactivity 5 < 6 > 7. Cyclisation onto silyl substituted alkynes occurs with similar ease to unsubstituted alkynes, desilylation occurring to give the same methyl substituted nitrone. Cyclisation onto alkyl substituted alkynes is more difficult than onto alk-1-ynes, but occurs cleanly at elevated temperatures. The available evidence supports the hypothesis that the hydroxylamine–alkyne reaction is one of a family of thermal ene-like reactions of which the *retro*-Cope elimination



49

Fig. 10



63

Fig. 11

Table 4 Infrared spectra of acacialactam and the synthetic lactam **49**

Acacialactam (neat) (cm^{-1})	Lactam **49** (CCl_4) (cm^{-1})
3350 (brs)	3400 (m)
1670 (s)	1665 (s)
1640 (s)	1620 (s)
1600 (s)	

Table 5 ^1H NMR Spectra of acacialactam and the synthetic lactam **49** in $CDCl_3$ (Fig. 10)

Assignment	Acacialactam (400 MHz) δ (ppm)	Lactam **49** (270 MHz) δ (ppm)
4-H	6.43 (ddd, *J* 7.3, 7.3 and 1.3)	6.13 (tq, *J* 4.5 and 1.6)
8-H	5.91 (dd, *J* 17.4 and 10.7)	5.81 (dd, *J* 17.1 and 10.4)
N-H	5.56 (br)	5.8 (br s)
9-H_A	5.24 (dd, *J* 17.4 and 1.0)	5.12 (dd, *J* 17.1 and 0.8)
9-H_B	5.10 (dd, *J* 10.7 and 1.0)	5.07 (dd, *J* 10.4 and 0.8)
5-H_2	2.25 (m)	2.37–2.31 (m)
10-H_3	1.85 (dd, *J* 2.2 and 1.0)	1.95 (q, *J* 1.6)
6-H_2	1.65 (m)	1.92–1.89 (m)
11-H	1.31 (s)	1.32 (s)

Table 6 ^{13}C NMR Spectra of acacialactam and the lactam **49** in $CDCl_3$ (Fig. 10)

Assignment	Acacialactam (100 MHz) δ (ppm)	Lactam **49** (67.5 MHz) δ (ppm)
C-2	171.5 (s)	170.0 (s)
C-4	144.6 (d)	142.0 (d)
C-8	137.7 (d)	136.4 (d)
C-3	129.9 (s)	130.9 (s)
C-9	112.3 (t)	113.2 (t)
C-7	73.0 (s)	56.5 (s)
C-5	40.8 (t)	38.1 (t)
C-10	28.0 (q)	30.1 (q)
C-6	23.2 (t)	27.4 (t)
C-11	12.7 (q)	22.5 (q)

reaction is a typical member, in which an N–O–H unit adds across a carbon-carbon multiple bond with a concerted pericyclic mechanism to give an *N*-oxide. The seven-membered lactam structure proposed for the natural product (±)-acacialactam was synthesised by use of a seven-membered nitrone constructed using a hydroxylamine–alkene cyclisation as the key step, and was shown to be incorrect.

Experimental

IR spectra were recorded on a Perkin-Elmer 1310 Spectrophotometer, calibrated relative to the absorption of polystyrene at 1603 cm^{-1}. The relative intensities of absorptions are indicated as: s, strong; m, medium; w, weak; br, broad. The ultraviolet spectrum of the lactam **49** was recorded on a Kontron Uvikon 940 spectrophotometer. ^1H NMR spectra were recorded on Varian EM-390 (90 MHz), Bruker WM-250, Bruker AC-250 (250 MHz), Bruker WP-80 (80 MHz), Bruker WM-400 (400 MHz) or JEOL JX-270 (270 MHz) instruments using an internal deuterium lock, or deuteriochloroform, or other indicated solvent as a reference. Chemical shifts (δ) are quoted in ppm relative to tetramethylsilane (δ 0). The multiplicities are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; td, triplet of doublets; br, broad; *etc.* Coupling constants (J) are quoted in Hz. ^{13}C NMR spectra were recorded on Bruker AM-400 (100 MHz) or JEOL JX-270 (67.5 MHz) instruments using an internal deuterium lock and proton decoupling. Chemical shifts (δ) are quoted relative to tetramethylsilane (δ 0). The multiplicities of the signals are indicated as: s, singlet; d, doublet; t, triplet; q, quartet. For spectra recorded at 100 MHz, an attached proton test (APT) was employed to distinguish between s and d, or d and q. The differentiation of signals within these groups is an interpretation based upon the chemical shift of the signal and the molecular structure. For spectra recorded at 67.5 MHz, distortion enhancement by polarisation transfer (DEPT) was employed to distinguish between s, t and d and q. The differentiation of d and q is an interpretation based on the chemical shift of the signal and the molecular structure. Some EI mass spectra were recorded on an A.E.I. MS 902 (low resolution spectra) or an A.E.I. MS 30 instrument (high resolution spectra) in conjunction with a DS 50S data system. CI, FAB and some EI mass spectra were recorded by the Mass Spectrometry Service at SmithKline Beecham Pharmaceuticals on a VG Fisons 302 (low resolution) or a JEOL JX-303 (high resolution) instrument, or by Dr J. Ballantine and co-workers at the SERC Mass Spectrometry Service at Swansea on a VG ZAB-E instrument. CI mass spectra were recorded using ammonia as the carrier gas. M.p.s were determined using a Büchi 510 melting point apparatus, and are uncorrected. Microanalyses were performed by the staff of the University Chemical Laboratory, or by the Microanalytical Service at SmithKline Beecham Pharmaceuticals. Analytical thin layer chromatography (TLC) was carried out on Merck silica plates pre-coated to a thickness of 0.25 mm with Kieselgel 60 PF_{254}. Preparative TLC (PLC) was carried out on silica plates coated to a thickness of 1 mm with Merck Kieselgel PF_{254}. Flash chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). HPLC was carried out with a Dynamax silica column.

Dry THF was distilled from potassium or sodium and benzophenone in a recycling still. Other dry solvents were purified by standard techniques.[50] Brine refers to a saturated aqueous solution of sodium chloride and ether refers to diethyl ether.

2-(But-3-enyl)-6-methyl-2,3,4,5-tetrahydropyridine 1-Oxide **3**[14] *and (2R*,5S*)-1-Hydroxy-2-methyl-5-(pent-4-ynyl)pyrrolidine* **4**.—A stirred solution of dec-1-en-9-yn-5-one oxime **1**[14] (500 mg, 3.03 mmol) in methanol (25 cm^3) was cooled to −10 °C under nitrogen. Sodium cyanoboranuide (421 mg, 6.06 mmol) and Methyl Orange indicator solution (2 drops), were then added. The solution was stirred at −10 °C under argon and hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise so as to just keep the solution pink. After 30 min, the solution was made strongly basic by the addition of 20% aq. sodium hydroxide and then poured into brine (50 cm^3) containing ice. The suspension was extracted with dichloromethane (4 × 30 cm^3), and the organic extracts of the hydroxylamine **5** [R_f 0.6, ethyl acetate–methanol (9:1)] were combined and stirred in the presence of sodium sulfate at 20 °C for 1 h. The solution was filtered and the filtrate was evaporated under reduced pressure. The mixture of products was purified by flash chromatography on a short silica column, eluting with ethyl acetate ⟶ ethyl acetate–methanol (9:1), to give the nitrone **3** as a pale yellow oil (336 mg, 67%), R_f 0.05, ethyl acetate–methanol (9:1); $\nu_{max}(CCl_4)/cm^{-1}$ 3080m (sp C–H), and 1640m (C=C); δ_H(90 MHz; $CDCl_3$) 5.9–5.7 (1 H, m, C*H*=CH_2), 5.0–4.9 (2 H, CH=C*H*$_2$), 3.7–3.6 (1 H, m, CH–N^+), 2.4–2.3 (2 H, m, CH_2C=N^+), 2.2–1.2 (8 H, m) and 2.0 (3 H, br s, Me); *m/z* (EI) 114 (52%), 96 (100), 82 (19), 67 (19), 55 (74) and 41 (77); *m/z* (CI) 168 (MH^+, 100%) and 152 (13) [Found: MH^+ 168.1388 (CI). $C_{10}H_{17}NO$ requires *MH* 168.1388]; and the crude pyrrolidine **4**, which was purified by flash chromatography on silica, eluting with hexane–ethyl acetate (4:1) to give the *pyrrolidine* **4** as a pale yellow oil (50 mg, 10%) which solidified on cooling to below 0 °C, R_f 0.55, ethyl acetate–methanol (9:1) (Found: C, 71.5; H, 10.1; N, 8.6. $C_{10}H_{17}NO$ requires C, 71.8; H, 10.3; N, 8.4%); $\nu_{max}(CCl_4)/cm^{-1}$ 3600s (O–H), 3310s (sp C–H), 3300brm (O–H) and 2120w (C≡C); δ_H(400 MHz; $CDCl_3$) 2.73–2.72 (1 H, m, MeC*H*), 2.64–2.63 (1 H, m, CH_2CHCH_2), 2.19–2.15 (2 H, m, CH_2C≡C), 1.99–1.93 (1 H, m), 1.91 (1 H, t, J 2.7, C≡C*H*), 1.89–1.78 (1 H, m), 1.52–1.32 (4 H, m), 1.28–1.24 (2 H, m) and 1.16 (3 H, d, J 6.2, Me); δ_C(100 MHz; $CDCl_3$) 84.35 (d), 68.37 (s), 67.94 (d), 63.69 (d), 33.33 (t), 27.19 (t), 25.63 (t), 25.30 (t), 16.79 (q) and 16.67 (t); *m/z* (EI) 150 (15%), 113 (13), 100 (100), 96 (28), 82 (21), 67 (14), 55 (22) and 41 (22); *m/z* (CI) 168 (MH^+,

100%), 166 (67), 152 (33) and 100 (12) [Found: MH^+ 168.1388 (CI). $C_{10}H_{17}NO$ requires *MH* 168.1388].

Cyclisation of the Hydroxylamine **2** *in the Absence of Oxygen with Galvinoxyl.*—A cold solution of the hydroxylamine **2** in dichloromethane containing sodium sulfate was prepared as above from the oxime **1**[14] (200 mg). Galvinoxyl (10 mg) was added and the solution freeze-thaw degassed three times and then allowed to warm to 20 °C under nitrogen. The reaction was monitored by TLC [hydroxylamine **2** R_f 0.60, ethyl acetate–methanol (9:1), nitrone **3** R_f 0.05, ethyl acetate–methanol (9:1)]. After 1 h, the reaction was complete by TLC. The suspension was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on a short silica column, eluting with ethyl acetate–methanol (9:1) to give the *nitrone* **3** as a pale yellow oil (135 mg, 67%).

2-(*But*-3-*enyl*)-2-(5-*trimethylsilylpent*-4-*ynyl*)-1,3-*dioxolane* **9**.—Butyllithium (1.1 mol dm^{-3} in hexane; 5 cm^3, 5.5 mmol) was added dropwise to a solution of the alkyne **8**[17] (1.00 g, 5.15 mmol) in dry THF (10 cm^3) at −78 °C under nitrogen. After 10 min, trimethylsilyl chloride (3.3 cm^3, 25.8 mmol) was added dropwise at −78 °C under nitrogen. The solution was warmed to 20 °C. After 30 min, sat. aq. ammonia (10 cm^3) was added dropwise at 20 °C under nitrogen. After 1 h, the mixture was poured into brine (50 cm^3) and the mixture was extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ethyl acetate (19:1) to give the *silylated alkyne* **9** as a colourless oil (1.36 g, 99%), R_f 0.35, hexane–ethyl acetate (19:1) (Found: C, 67.7; H, 10.0. $C_{15}H_{26}O_2Si$ requires C, 67.6; H, 9.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (sp^2 C–H), 2180s (C≡C) and 1640m (C=C); δ_H(250 MHz; $CDCl_3$) 5.83–5.76 (1 H, m, C*H*=CH_2), 5.05–5.04, 4.98–4.95 and 4.91–4.90 (2 H, 3 × m, CH=CH_2), 3.93 (4 H, s, OCH_2CH_2O), 2.23 (2 H, t, *J* 6.9, $CH_2C{\equiv}C$), 2.14–2.07 (2 H, m, CH_2CH=CH_2), 1.74–1.66 (4 H, m, $CH_2CO_2CH_2$), 1.64–1.54 (2 H, m, CH_2-CH_2CH_2) and 0.13 (9 H, s, Me_3Si); δ_C(100 MHz; $CDCl_3$) 136.5 (d), 114.3 (t), 111.2 (s), 107.1 (s), 84.7 (s), 64.7 (t), 36.2 (t), 36.1 (t), 28.0 (t), 23.1 (t), 20.0 (t) and 0.1 (q); *m/z* (EI) 211 (39%), 127 (100), 99 (54), 83 (12), 73 (24) and 55 (27); *m/z* (CI) 267 (MH^+, 57%), 223 (100), 211 (52), 151 (23), 133 (21), 127 (100), 117 (43), 99 (50) and 90 (100) [Found: MH^+ 267.1780 (CI). $C_{15}H_{26}O_2Si$ requires *M*H 267.1780].

2-(*But*-3-*enyl*)-2-(5-tert-*butyldimethylsilylpent*-4-*ynyl*)-1,3-*dioxolane* **10**.—Butyllithium (1.4 mol dm^{-3} in hexane; 0.85 cm^3, 1.19 mmol) was added dropwise to a stirred solution of the alkyne **8**[17] (210 mg, 1.08 mmol) in dry THF (5 cm^3) at −78 °C under nitrogen. After 10 min, a solution of *tert*-butyl dimethylsilyl chloride (326 mg, 216 mmol) in THF (5 cm^3) was added dropwise at −78 °C under nitrogen. The solution was warmed to 20 °C. After 30 min, sat. aq. ammonia (10 cm^3) was added dropwise at 20 °C under nitrogen. After 1 h, the mixture was poured into brine (20 cm^3) and the mixture was extracted with dichloromethane (3 × 20 cm^3). The organic layers were washed with brine (20 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The compound was purified by PLC on silica, eluting with hexane–ether (19:1), using two elutions, to give the *silylated alkyne* **10** as a colourless oil (181 mg, 54%), R_f 0.45, hexane–ether (4:1) (Found: C, 70.3; H, 10.6. $C_{18}H_{32}O_2Si$ requires C, 70.1; H, 10.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (sp^2 C–H), 2180s (C≡C) and 1640m (C=C); δ_H(250 MHz; $CDCl_3$) 5.87–5.75 (1 H, m, C*H*=CH_2), 5.04–5.03, 4.97–4.94 and 4.91–4.90 (2 H, 3 × m, CH=CH_2), 3.92 (4 H, s, OCH_2CH_2O), 2.24 (2 H, t, *J* 6.8, $CH_2C{\equiv}C$), 2.13–2.09 (2 H, m, CH_2CH=CH_2), 1.73–1.66 (4 H, m, $CH_2CO_2CH_2$), 1.60–1.56 (2 H, m, $CH_2CH_2CH_2$), 0.91 (9 H, s, Me_3C) and 0.06 (6 H, s, Me_2Si); δ_C(100 MHz; $CDCl_3$) 138.5 (d), 114.2 (t), 111.2 (s), 107.6 (s), 82.8 (s), 64.9 (t), 36.2 (t), 36.1 (t), 20.0 (t), 28.1 (q), 23.2 (t), 20.0 (t), 16.5 (s) and −4.5 (q); *m/z* (EI) 253 (32%), 207 (29), 127 (100), 99 (40), 75 (39) and 55 (18); *m/z* (CI) 309 (MH^+, 100%), 265 (45), 253 (14), 207 (12), 159 (67), 151 (34), 132 (42), 127 (29), 99 (12) and 91 (12) [Found: MH^+ 309.2250 (CI). $C_{18}H_{32}O_2Si$ requires *M*H 309.2250].

10-(*Trimethylsilyl*)*dec*-1-*en*-9-*yn*-5-*one Oxime* **11**.—Hydroxylamine hydrochloride (1.1 g, 15 mmol) and Methyl Orange indicator (2 drops) were added to a stirred solution of the 1,3-dioxolane **9** (1.36 g, 5.11 mmol) in ethanol (10 cm^3). The suspension was acidified with aq. hydrochloric acid (2 mol dm^{-3}) until the pink solution ceased to change colour. After 6 h, the solution was poured into brine (50 cm^3) and the mixture was extracted with dichloromethane (3 × 30 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ether (4:1) to give the *oxime* **11** as a colourless oil (1.08 mg, 89%), an approximately 1:1 mixture of *E* and *Z* oximes, R_f 0.20, hexane–ether (4:1) (Found: C, 66.0; H, 9.7; N, 5.8. C_{13}-$H_{24}NOSi$ requires C, 65.8; H, 9.8; N, 5.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610s (O–H), 3280brm (O–H), 3080m (sp^2 C–H), 2180s (C≡C) and 1640m (C=C); δ_H(250 MHz; $CDCl_3$) 5.86–5.76 (1 H, m, C*H*=CH_2), 5.09–5.07, 5.03–5.00 and 4.97–4.96 (2 H, 3 × m, CH=CH_2), 2.48–2.40 (2 H, m), 2.33–2.44 (6 H, m), 1.78–1.69 (2 H, m, $CH_2CH_2CH_2$) and 0.14 (9 H, s, Me_3Si); δ_C(100 MHz; $CDCl_3$) 160.2 (s), 137.5 (d), 137.2 (d), 115.3 (t), 115.2 (t), 106.6 (s), 106.5 (s), 85.2 (s), 33.6 (t), 33.0 (t), 30.2 (t), 29.5 (t), 27.1 (t), 26.9 (t), 25.0 (t), 24.6 (t), 20.0 (t), 19.4 (t) and 0.1 (q); *m/z* (EI) 220 (12%), 208 (11), 148 (12), 113 (26), 96 (20), 81 (27), 73 (100) and 55 (73); *m/z* (CI) 238 (MH^+, 100%), 222 (47), 148 (11), 113 (12) and 90 (19) [Found: $(M + NH_4)^+$ 238.1627 (CI). $C_{13}H_{24}NOSi$ requires $(M + NH_4)$ 238.1627].

10-(tert-*Butyldimethylsilyl*)*dec*-1-*en*-9-*yn*-5-*one Oxime* **12**.—Hydroxylamine hydrochloride (243 mg, 3.50 mmol) was added to a stirred solution of the 1,3-dioxolane **10** (540 mg, 1.75 mmol) and two drops of Methyl Orange indicator solution in ethanol (10 cm^3). The suspension was acidified with aq. hydrochloric acid (2 mol dm^{-3}) until the pink colour ceased to change. After 18 h, the solution was poured into water (50 cm^3) and the suspension was extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (17:3) to give the *oxime* **12**, an approximately 1:1 mixture of *E* and *Z* oximes, as a pale yellow oil (481 mg, 98%), R_f 0.20, hexane–ether (4:1) (Found: C, 69.0; H, 10.4; N, 4.9. $C_{16}H_{29}NOSi$ requires C, 68.8; H, 10.5; N, 5.0%); ν_{max}-$(CCl_4)/cm^{-1}$ 3610m (O–H), 3300brm (O–H), 3080w (sp C–H), 2180s (C≡C) and 1640m (C=C); δ_H(250 MHz; $CDCl_3$) 5.90–5.74 (1 H, m, C*H*=CH_2), 5.10–5.07, 5.03–5.00 and 5.97–5.96 (2 H, 3 × m, CH=CH_2), 2.48–2.41 (2 H, m, $CH_2C{\equiv}C$), 2.34–2.22 (6 H, m), 1.80–1.67 (2 H, m, $CH_2CH_2CH_2$), 0.92 and 0.91 (9 H, 2 s, Me_3C) and 0.07 (6 H, 2 s, Me_2Si); δ_C(100 MHz; $CDCl_3$) 160.4 (s), 137.5 (d), 137.3 (d), 115.3 (t), 115.2 (t), 107.1 (s), 107.0 (s), 83.3 (s), 33.7 (t), 33.1 (t), 30.2 (t), 29.6 (t), 27.2 (t), 27.0 (t), 26.1 (q), 25.2 (t), 24.8 (t), 20.1 (t), 19.5 (t), 16.5 (s) and −4.5 (q); *m/z* (EI) 150 (12%), 96 (13), 75 (95), 55 (100) and 41 (26); *m/z* (CI) 280 (MH^+, 100%) and 264 (29) [Found: MH^+ 280.2097 (CI). $C_{16}H_{29}NOSi$ requires *M*H 280.2097].

Reductive Cyclisation of the Oxime **11**.—A stirred solution of oxime **11** (134 mg, 0.57 mmol) in methanol (10 cm^3) was cooled

to −10 °C under nitrogen. Sodium cyanoboranuide (71 mg, 1.13 mmol) and universal indicator solution (5 drops) were added. The solution was stirred at −10 °C under nitrogen and then hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise so as to just keep the solution pink. After 30 min, the solution was neutralised with sat. aq. ammonia and then poured into brine (20 cm^3) containing ice. The suspension was extracted with dichloromethane (4 × 20 cm^3) and the combined organic extracts were stirred in the presence of anhydrous sodium sulfate for 1 h. The solution was then filtered and the solvent evaporated under reduced pressure. The compound was purified by flash chromatography, eluting with ethyl acetate ⟶ ethyl acetate–methanol (9:1) to give the *nitrone* **3** as a pale yellow oil (65 mg, 69%).

Reductive Cyclisations of the Oxime **12**.—(*a*) Hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise to a stirred solution of the oxime **12** (91 mg, 0.33 mmol), sodium cyanoboranuide (41 mg, 0.65 mmol) and Methyl Orange indicator solution (2 drops) in methanol (5 cm^3) at −10 °C under nitrogen, so as to just keep the solution pink. After 30 min, the solution was neutralised with aq. ammonia, the suspension was poured into brine (20 cm^3) containing ice and the supension extracted with dichloromethane (4 × 20 cm^3). The organic extracts were combined and the solution was stirred at 20 °C in the presence of anhydrous sodium sulfate at 20 °C for 1 h. The solution was filtered and, after removal of the solvent under reduced pressure, the compound was purified by flash chromatography on a short silica column, eluting with ethyl acetate followed by ethyl acetate–methanol (9:1) to give the *nitrone* **3** as a pale yellow oil (62%).

(*b*) N-[10-(tert-*Butyldimethylsilyl*)*dec*-1-*en*-9-*yn*-5-*yl*]*hydroxylamine* **14**. The procedure was followed as for (*a*), but using the oxime **12** (100 mg, 0.36 mmol) and sodium cyanoboranuide (68 mg, 1.08 mmol) and extracting with $CDCl_3$ (0.5 cm^3). The organic layer was separated and filtered through magnesium sulfate into an NMR tube. The solution was frozen in an acetone–solid carbon dioxide bath and the following spectrum was recorded immediately on warming: δ_H(250 MHz; $CDCl_3$) 5.91–5.71 (1 H, m, C*H*=CH_2), 5.07–5.04, 5.00–4.96 and 4.95–4.91 (2 H, 3 × m, CH=CH_2), 2.91–2.78 (1 H, m, CHN), 2.31–2.20 (2 H, m, CH_2C≡C), 2.16–2.05 (2 H, m, CH_2CH=CH_2), 1.73–1.40 (6 H, m), 0.95 (9 H, s, Me_3C) and 0.07 (6 H, s, Me_2Si).

2-(*But*-3-*enyl*)-2-(*hex*-4-*ynyl*)-1,3-*dioxolane* **17**.—Butyllithium (1.1 mol dm^{-3} in hexane; 2.9 cm^3, 3.3 mmol) was added dropwise to a solution of the alkyne **8**[17] (576 mg, 2.97 mmol) in dry THF (10 cm^3) at −10 °C under nitrogen. After 10 min, dry TMEDA (0.9 cm^3, 5.9 mmol) was added dropwise at −10 °C under nitrogen and after a further 10 min, iodomethane (0.56 cm^3, 8.91 mmol), dried by passage through an alumina column, was added dropwise, also at −10 °C under nitrogen, immediately producing a white precipitate. After 1 h, sat. aq. ammonia (5 cm^3) was added dropwise at −10 °C. The mixture was warmed to 20 °C and stirred for 1 h at this temp. The mixture was then poured into water (20 cm^3) and extracted with ether (3 × 20 cm^3). The organic layers were washed with water (20 cm^3), combined, dried ($MgSO_4$) and evaporated under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ethyl acetate (19:1) to give the *methylated alkyne* **17** as a colourless oil (568 mg, 92%), R_f 0.45, hexane–ether (8:2) (Found: C, 75.1; H, 9.8. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080m (sp^2 C–H) and 1640m (C=C); δ_H(250 MHz; $CDCl_3$) 5.83–5.79 (1 H, m, C*H*=CH_2), 5.04–5.02, 4.98–4.96, 4.95–4.93 and 4.91–4.89 (2 H, 4 × m, CH=CH_2), 3.92 (4 H, s, OCH_2CH_2O), 2.06–2.16 (4 H, m, C≡CCH_2 and CH_2=CHCH_2), 1.75 (3 H, t, *J* 2.6, Me), 1.73–1.63 (4 H, m, $CH_2CO_2CH_2$) and 1.49–1.59 (2 H, m, $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 138.5 (d), 114.2 (t), 111.2 (s), 78.8 (s), 75.7 (s), 65.0 (t), 36.4 (t), 28.1 (t), 23.4 (t), 18.9 (t) and 3.4 (q); *m*/*z* (EI) 153 (100%), 127 (83), 99 (29), 55 (84) and 41 (47); *m*/*z* (CI) 209 (MH^+, 12%), 153 (72), 127 (100), 99 (14), 55 (28) and 39 (18) [Found: MH^+ 209.1542 (CI). $C_{13}H_{20}O_2$ requires *M*H 209.1542].

Undec-1-*en*-9-*yn*-5-*one Oxime* **18**.—Hydroxylamine hydrochloride (569 mg, 8.19 mmol) was added to a stirred solution of the 1,3-dioxolane **17** (568 mg, 2.73 mmol) and Methyl Orange indicator (1 drop) in ethanol (10 cm^3). Aq. hydrochloric acid (2 mol dm^{-3}) was added until the pink suspension ceased to change colour and then water was added until all the hydroxylamine hydrochloride had dissolved. After 48 h, the solution was poured into water (25 cm^3) and the mixture was extracted with dichloromethane (3 × 25 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ether (4:1) to give the *oxime* **18** as a colourless oil (415 mg, 79%), an approximately 1:1 mixture of *E* and *Z* oximes, R_f 0.20 hexane–ether (4:1) (Found: C, 73.6; H, 9.4; N, 7.6. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.6; N, 7.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610m (O–H), 3300brm (O–H), 3080m (sp^2 C–H) and 1640m (C=C); δ_H(250 MHz; $CDCl_3$) 5.89–5.75 (1 H, m, C*H*=CH_2), 5.10–5.08, 5.03–5.00 and 4.98–4.96 (2 H, 3 × m, CH=CH_2), 2.48–2.39 (2 H, m), 2.34–2.23 (4 H, m), 2.23–2.13 (2 H, m), 1.77 and 1.76 (3 H, t, *J* 2.5 and t, *J* 2.5, Me) and 1.75–1.65 (2 H, m, $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 160.4 (s), 137.6 (d), 137.35 (d), 115.3 (t), 115.1 (t), 78.4 (s), 78.3 (s), 76.2 (s), 76.2 (s), 33.6 (t), 33.3 (t), 30.2 (t), 29.6 (t), 27.1 (t), 27.1 (t), 25.4 (t), 25.0 (t), 19.0 (t), 18.4 (t) and 3.4 (q); *m*/*z* (EI) 162 (20%), 150 (25), 134 (23), 122 (14), 113 (49), 98 (26), 91 (17), 81 (42), 79 (43), 77 (30), 67 (41), 53 (86) and 41 (100); *m*/*z* (CI) 180 (MH^+, 100%) and 164 (12) [Found: M^+ 179.1310 (EI). $C_{11}H_{17}NO$ requires *M* 179.1310].

(2R*,5S*)-1-*Hydroxy*-2-(*hex*-4-*ynyl*)-5-*methylpyrrolidine* **20** *and* (2R*,5R*)-1-*Hydroxy*-2-(*hex*-4-*ynyl*)-5-*methylpyrrolidine* **21**.—A solution of the oxime **18** (115 mg, 0.64 mmol) in methanol (10 cm^3) was cooled to −10 °C under nitrogen. Sodium cyanoboranuide (80 mg, 1.28 mmol) and Methyl Orange indicator solution (2 drops) were added. The solution was stirred at −10 °C under nitrogen and hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise so as to just keep the solution pink. After 30 min, the solution was made strongly basic with 20% aq. sodium hydroxide and poured into brine (20 cm^3) containing ice. The suspension was extracted with dichloromethane (4 × 15 cm^3) and the ice cold organic extracts were combined and sodium sulfate was added. The suspension was freeze-thaw degassed three times and allowed to warm to 20 °C under nitrogen. The suspension was stirred at 20 °C under nitrogen for 20 h, then filtered and the filtrate evaporated under reduced pressure. The mixture of products was purified by flash chromatography, eluting with hexane–ether (7:3), to give the cis-*pyrrolidine* **20** as a white solid (29 mg, 25%), m.p. 52–53 °C (no suitable solvent for recrystallisation could be found); R_f 0.30, ether–hexane (1:1) (Found: C, 72.8; H, 10.7; N, 7.9. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610s (O–H) and 3260brm (O–H); δ_H(250 MHz; $CDCl_3$) 2.78–2.62 (2 H, m, CHN), 2.16–2.09 (2 H, m, CH_2C≡C), 1.98–1.77 (3 H, m), 1.75 (3 H, t, *J* 2.6, C≡CMe), 1.53–1.21 (5 H, m) and 1.18 (3 H, d, *J* 6.2, CH*Me*); δ_C(100 MHz; $CDCl_3$) 79.1 (s), 75.6 (s), 67.9 (d), 63.6 (d), 33.5 (t), 27.2 (t), 26.2 (t), 25.3 (t), 19.0 (q), 18.8 (t) and 3.5 (q); *m*/*z* (EI) 164 (13%), 126 (40), 100 (100), 82 (17), 79 (13), 77 (11), 67 (24), 53 (28) and 41 (35); *m*/*z* (CI) 182 (MH^+, 100%) and 100 (14) [Found: M^+ 181.1467 (EI). $C_{11}H_{19}NO$ requires *M* 181.1467]; and the trans-*pyrrolidine* **21** as a pale yellow oil (68 mg, 58%), R_f 0.15, 1:1

ether–hexane (Found: C, 73.0; H, 10.6; N, 7.6. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610m (O–H) and 3240brm (O–H); δ_H(250 MHz; $CDCl_3$) 3.29–3.21 (1 H, m, C*H*Me), 3.09–3.04 (1 H, m, CH_2CHNCH_2), 2.12–2.05 (2 H, m, $CH_2C{\equiv}C$), 1.98–1.75 (3 H, m), 1.71 (3 H, t, *J* 2.5, C≡CMe), 1.54–1.37 (5 H, m) and 1.94 (3 H, d, *J* 6.7, CH*Me*); δ_C(100 MHz; $CDCl_3$) 78.9 (s), 75.5 (s), 65.8 (br d), 61.5 (br d), 32 (br), 28.7 (t), 27.3 (t), 26.6 (t), 18.9 (t), 16 (br) and 3.4 (q).

2-(*Hex*-5-*ynyloxy*)*tetrahydropyran* **23**.—4,5-Dihydropyran (12.8 cm^3, 142 mmol) was added to a stirred solution of hex-5-yn-1-ol **22** (4.64 g, 47.3 mmol) and methylbenzenesulfonic acid (100 mg, cat.) in dry dichloromethane (50 cm^3) at 0 °C. After 1.25 h, ethyl acetate (100 cm^3) was added, and the solution was poured into sat. aq. sodium hydrogen carbonate (250 cm^3). Ethyl acetate (100 cm^3) was then added, the layers separated, the organic layer was washed with brine (250 cm^3) and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ethyl acetate (24:1) to give the *tetrahydropyranyl ether* **23** as a colourless oil (8.68 g, 100%), R_f 0.50, hexane–ethyl acetate (4:1) (Found: C, 72.8; H, 10.0. $C_{11}H_{18}O_2$ requires C, 72.5; H, 10.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 33.10s (sp C–H) and 2120w (C≡C); δ_H(400 MHz; C_6D_6) 4.52 (1 H, t, *J* 3.3, OCHO), 3.78–3.69 (2 H, m, CH_2O in side-chain), 3.38–3.35 (1 H, m, C*H*HO in ring), 3.24–3.19 (1 H, m, CH*H*O in ring), 1.98 (2 H, td, *J* 7.1 and 2.7, $CH_2C{\equiv}C$), 1.77 (1 H, t, *J* 2.7, C≡CH) and 1.75–1.21 (10 H, m); δ_C(100 MHz; C_6D_6) 98.5 (d), 84.3 (d), 68.94 (s), 66.76 (t), 61.53 (t), 31.00 (t), 29.16 (t), 25.9 (t), 25.8 (t), 19.6 (t) and 18.4 (t); *m/z* (EI) 101 (17%), 85 (100), 81 (53), 79 (30), 67 (22), 57 (17), 56 (26), 55 (23), 53 (19) and 41 (38); *m/z* (CI) 200 [$(M + NH_4)^+$, 3%], 183 (MH^+, 3), 102 (100) and 85 (100) [Found: $(M + NH_4)^+$ 200.1651 (CI). $C_{11}H_{18}O_2$ requires $(M + NH_4)$ 200.1651].

2-(*Hept*-5-*ynyloxy*)*tetrahydropyran* **24**.[51]—Butyllithium (1.5 mol dm^{-3} in hexane; 25.6 cm^3, 38.44 mmol) was added dropwise to a solution of the alkyne **23** (6.36 g, 35.0 mmol) in dry THF (100 cm^3) at −10 °C under nitrogen. After 10 min, TMEDA (11.6 cm^3, 76.9 mmol) was added dropwise under nitrogen at −10 °C. After a further 10 min, iodomethane (10.9 cm^3, 175 mmol), passed immediately before use through an alumina column, was added in one portion under nitrogen. The temperature rose to 15 °C and a white precipitate formed rapidly. After 1 h, the suspension was poured into water (100 cm^3), the mixture was extracted with ethyl acetate (3 × 100 cm^3) and the combined organic layers were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ethyl acetate (26:1) to give the *methylated alkyne* **24** as a colourless oil (6.04 g, 88%), R_f 0.50, hexane–ethyl acetate (4:1) (Found: C, 73.4; H, 10.2. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.3%); $\nu_{max}(CCl_4)$ no bands other than sp^3 C–H stretches above 1500 cm^{-1}; δ_H(250 MHz; C_6D_6) 4.55 (1 H, t, *J* 3.3, OCHO), 3.83–3.74 (2 H, m, CH_2O in side chain), 3.42–3.23 (2 H, m, CH_2O in ring), 2.15–2.07 (2 H, m, $CH_2C{\equiv}C$), 1.81–1.51 (6 H, m), 1.55 (3 H, t, *J* 2.6, MeC≡C) and 1.45–1.18 (4 H, m); δ_C(100 MHz; C_6D_6) 99.5 (d), 79.3 (s), 75.8 (s), 66.9 (t), 61.5 (t), 31.0 (t), 29.4 (t), 26.4 (t), 26.0 (t), 19.6 (t), 17.0 (t) and 3.4 (q); *m/z* (EI) 197 (MH^+, 5%), 125 (13), 112 (16), 101 (22), 95 (96), 85 (100), 79 (24), 67 (93), 55 (54) and 41 (56); *m/z* (CI) 214 [$(M + NH_4)^+$, 3%], 197 (MH^+, 7%), 102 (96), 95 (32) and 85 (100) [Found: MH^+ 197.1542 (CI). $C_{12}H_{20}O_2$ requires *M*H 197.1542].

Hept-5-*yn*-1-*ol* **25**.[51]—A solution of the tetrahydropyranyl ether **24** (6.04 g, 30.8 mmol) and 4-methylbenzenesulfonic acid (100 mg, cat.) in methanol (250 cm^3) was stirred for 2.5 h at 20 °C. Sat. aq. sodium hydrogen carbonate (50 cm^3) was added, the white suspension was poured into water (200 cm^3), and the mixture was extracted with dichloromethane (3 × 250 cm^3). The combined organic layers were then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (9:1) to give hept-5-yn-1-ol **25** as a colourless oil (3.40 g, 98%), R_f 0.15 (8:2 hexane–ethyl acetate) (Found: C, 74.7; H, 10.9. $C_7H_{12}O$ requires C, 75.0; H, 10.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610m (O–H) and 3500brw (O–H); δ_H(250 MHz; $CDCl_3$) 3.65 (2 H, t, *J* 6.3, CH_2O), 2.20–2.11 (2 H, m, $CH_2C{\equiv}C$), 1.76 (3 H, t, *J* 2.5, C≡CMe) and 1.72–1.47 (4 H, m); δ_C(100 MHz; $CDCl_3$) 78.9 (s), 75.8 (s), 62.5 (t), 31.8 (t), 25.2 (t), 18.5 (t) and 3.4 (q); *m/z* (EI) 97 (13%), 91 (10), 84 (52), 79 (49), 77 (36), 68 (100), 53 (38) and 39 (50); *m/z* (CI) 113 (MH^+, 100%) and 68 (41) [Found: MH^+ 113.0966 (CI). $C_7H_{12}O$ requires *M*H 113.0966].

Hept-5-*ynal Oxime* **26**.—A solution of hept-5-yn-1-ol **25** (429 mg, 3.83 mmol) in dry dichloromethane (5 cm^3) was added dropwise to a stirred suspension of PCC (1.24 g, 5.75 mmol) and powdered, activated 3 Å molecular sieves (100 mg) in dry dichloromethane (5 cm^3). After 4 h, the suspension was filtered through a Florisil column and the solvent was removed under reduced pressure. Pyridine–ethanol (1:1; 10 cm^3) and hydroxylamine hydrochloride (799 mg, 11.5 mmol) were added and the solution was stirred for 15 min at 20 °C. The solution was poured into hydrochloric acid (2 mol dm^{-3}; 20 cm^3) and the mixture was extracted with dichloromethane (4 × 20 cm^3). The combined organic layers were then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography, eluting with dichloromethane [hexane–ether (4:1) is also suitable], and recrystallisation from hexane to give *hept*-5-*ynal oxime* **26**, a mixture (2:1) of *E* and *Z* oximes, as white needles (300 mg, 63%), m.p. 65–67 °C; R_f 0.40 and 0.50, dichloromethane–ether (9:1) (Found: C, 67.2; H, 8.9; N, 11.2. $C_7H_{11}NO$ requires C, 67.2; H, 8.9; N, 11.2%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610s (O–H), 3300brs (O–H), 3080w (sp^2 C–H) and 3040w (sp^2 C–H); δ_H(250 MHz; $CDCl_3$) 7.39 and 6.71 (1 H, t, *J* 6.0 and t, *J* 6.0, CH=N), 2.43 and 2.27 (2 H, td, *J* 7.3 and 6.0 and td, *J* 7.3 and 6.0, $CH_2CH{=}N$), 2.22–2.09 (2 H, m, $CH_2C{\equiv}C$), 1.72 (3 H, t, *J* 2.5, Me) and 1.63 and 1.62 (2 H, quintet, *J* 7.3 and quintet, *J* 7.3, $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 152.0 (d), 151.5 (d), 78.1 (s), 78.0 (s), 76.4 (s), 76.3 (s), 28.6 (t), 25.8 (t), 25.5 (t), 24.3 (t), 18.6 (t), 18.2 (t) and 3.4 (q); *m/z* (CI) 126 [MH^+, 71%], 108 (48), 95 (48), 84 (50), 81 (48), 79 (47), 67 (61), 55 (54), 53 (65), 50 (48) and 41 (100) [Found: MH^+ 126.0919 (CI). $C_7H_{11}NO$ requires *M*H 126.0919].

6-*Ethyl*-2,3,4,5-*tetrahydropyridine* 1-*Oxide* **28**.—Hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise to a stirred solution of the oxime **26** (100 mg, 0.80 mmol), sodium cyanoboranuide (151 mg, 2.40 mmol) and Methyl Orange solution (1 drop) in methanol (5 cm^3) at −10 °C under nitrogen, so as to just keep the solution pink. After 30 min, the solution was basified with aq. 20% sodium hydroxide, the suspension was poured into brine (20 cm^3) containing ice and then the suspension was extracted with dichloromethane (4 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), the solvent was removed under reduced pressure, and toluene (20 cm^3) was added. The solution was refluxed under nitrogen for 2 h. After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on a short silica column, eluting with ethyl acetate followed by ethyl acetate–methanol (17:3) to give the *nitrone* **28** as a pale yellow oil (94 mg, 94%), R_f 0.10, ethyl acetate–methanol; $\nu_{max}(CCl_4)/cm^{-1}$ 1600m (C=N^+); δ_H(250 MHz; $CDCl_3$) 3.76 (2

H, t, *J* 6.0, CH_2N^+), 2.53 (2 H, q, *J* 7.6, CH_2Me), 2.38 (2 H, t, *J* 6.2, $CH_2CH_2C{=}N^+$), 1.93–1.83 (2 H, m, $CH_2CH_2N^+$), 1.74–1.64 (2 H, m, $CH_2CH_2C{=}N^+$) and 1.07 (3 H, t, *J* 7.6); δ_C(100 MHz; $CDCl_3$) 150.18 (s), 57.86 (t), 27.78 (t), 24.65 (t), 22.93 (t), 18.57 (t) and 8.69 (q); *m/z* (EI) 127 (M^+, 67%), 110 (12), 82 (15) and 55 (100) [Found: M^+ 127.0997 (EI). $C_7H_{13}NO$ requires *M* 127.0997].

3-[4-(*Trimethylsilyl*)*but*-3-*ynyl*]*cyclohex*-2-*enone* **30**.—A solution of 4-bromo-1-(trimethylsilyl)but-1-yne **29**[52] (12.8 g, 62.1 mmol) in dry THF (130 cm^3) was added dropwise to magnesium turnings (1.81 g, 74.5 mmol) under nitrogen. The Grignard reaction was initiated immediately. After 1 h, the stirred solution was cooled to 0 °C. A white precipitate of the Grignard reagent formed. A solution of 3-ethoxycyclohex-2-enone (9.60 g, 68.3 mmol) in dry THF (70 cm^3) was added dropwise at 0 °C under nitrogen. The solution was warmed to 20 °C and stirred for 14 h at 20 °C under nitrogen, then quenched with 15% aq. acetic acid (150 cm^3) and stirred for a further 2 h at 20 °C. The aqueous layer was then separated and extracted with dichloromethane (2 × 250 cm^3). The organic layers were combined and most of the solvent was removed under reduced pressure. Sat. aq. sodium hydrogen carbonate (150 cm^3) was added and then solid sodium hydrogen carbonate was added until effervescence ceased. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 250 cm^3). The combined organic layers were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (3:7) to give the *enone* **30** as a pale yellow oil (9.36 g, 68%), R_f 0.30, ether–hexane (1:1) (Found: C, 70.9; H, 9.3. $C_{13}H_{20}OSi$ requires C, 70.9; H, 9.2%); ν_{max}(CCl_4)/cm^{-1} 2180s (C≡C), 1700s (α,β-unsaturated ketone) and 1620m (α,β-unsaturated ketone); δ_H(250 MHz; $CDCl_3$) 5.88 (1 H, s, C=CH), 2.42 (4 H, s, $CH_2CH_2C{\equiv}C$), 2.38–2.28 (4 H, m, 1.98 (2 H, quintet, *J* 6.4, $CH_2CH_2CH_2$) and 0.12 (9 H, s, Me_3Si); δ_C(100 MHz; $CDCl_3$) 199.6 (s), 163.8 (s), 126.4 (d), 105.0 (s), 86.1 (s), 37.3 (t), 36.6 (t), 29.5 (t), 22.6 (t), 16.0 (t) and 0.0 (q); *m/z* (EI) 205 (12%), 177 (19), 163 (12), 118 (41), 105 (13), 91 (15), 81 (37), 75 (82) and 73 (100); *m/z* (CI) 238 [$(M + NH_4)^+$, 13%] and 221 (MH^+, 100) [Found: MH^+ 221.1362 (CI). $C_{13}H_{20}OSi$ requires *M*H 221.1362].

3-(*But*-3-*ynyl*)-2,3-*epoxycyclohexanone* **31**.—20% Aq. sodium hydroxide (1 cm^3, cat.) was added to a stirred solution of the enone **30** (10.7 g, 49 mmol) in methanol (100 cm^3). After 4 h, 30% aq. hydrogen peroxide (30 cm^3) was added. After 15 min, the solution was poured into brine (200 cm^3) and the suspension was extracted with dichloromethane (3 × 200 cm^3). The combined organic layers were then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (3:1) to give the *epoxide* **31** as a pale yellow oil (5.84 g, 73%), R_f 0.40, ether–hexane (1:1) (Found: C, 73.2; H, 7.5. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.4%); ν_{max}(CCl_4)/cm^{-1} 3310s (sp C–H), 2120m (C≡C) and 1715s (C=O); δ_H(250 MHz; $CDCl_3$) 3.17 (1 H, s, CHO) and 2.54–1.58 (11 H, m); δ_C(100 MHz; $CDCl_3$) 206.2 (s), 82.6 (s), 69.6 (d), 64.1 (s), 61.0 (d), 35.8 (t), 34.4 (t), 26.1 (t), 17.1 (t) and 14.1 (t); *m/z* (EI) 135 (12%), 125 (20), 112 (23), 108 (35), 97 (62), 91 (52), 79 (96), 67 (30), 55 (90) and 41 (100); *m/z* (CI) 182 [$(M + NH_4)^+$, 100%], 165 (MH^+, 15) and 149 (15) [Found: $(M + NH_4)^+$ 182.1181 (CI). $C_{10}H_{12}O_2$ requires $(M + NH_4)$ 182.1181].

Deca-1,9-*diyn*-5-*one* **32**.—4-Methylbenzenesulfonohydrazide (6.63 g, 35.6 mmol) was added to a stirred solution of the epoxide **31** (5.84 g, 35.6 mmol) in dichloromethane–acetic acid (1:1; 100 cm^3) at −25 °C. After 18 h, the white suspension was warmed to 20 °C for 1 h, then to 45 °C for 3 h, during which time the white precipitate dissolved and nitrogen was evolved. The solution was poured into sat. aq. sodium hydrogen carbonate (250 cm^3) and solid sodium hydrogen carbonate was added until effervescence ceased. The mixture was extracted with dichloromethane (3 × 250 cm^3). The combined organic layers were dried ($MgSO_4$). After removal of most of the solvent under reduced pressure, silica gel (10 g) was added, and the rest of the solvent was removed under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ether (19:1) to give the *deca*-1,9-*diyn*-5-*one* **32** as a colourless oil (2.56 g, 49%), R_f 0.45, ether–hexane (1:1) (Found: C, 81.0; H, 8.3. $C_{10}H_{12}O$ requires C, 81.0; H, 8.2%); ν_{max}(CCl_4)/cm^{-1} 3310s (sq C–H), 2120m (C≡C) and 1715s (C=O); δ_H(400 MHz; $CDCl_3$) 2.66 (2 H, t, *J* 7.2, $COCH_2CH_2C{\equiv}C$), 2.57 (2 H, t, *J* 7.2, $COCH_2CH_2CH_2$), 2.43 (2 H, td, *J* 7.2 and 1.1, $COCH_2CH_2C{\equiv}C$), 2.21 (2 H, td, *J* 7.2 and 1.1, $COCH_2CH_2CH_2$), 1.95–1.92 (2 H, m, C≡CH) and 1.79 (2 H, quintet, *J* 7.2, $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 207.8 (s), 83.4 (s), 83.0 (s), 69.13 (d), 63.73 (d), 41.4 (t), 41.1 (t), 22.1 (t), 17.7 (t) and 12.9 (t); *m/z* (CI) 149 (MH^+, 22%), 109 (64), 95 (87), 81 (88), 67 (53) and 53 (100) [Found: MH^+ 149.0966 (CI). $C_{10}H_{12}O$ requires *M*H 149.0966].

Deca-1,9-*diyn*-5-*one Oxime* **33**.—Hydroxylamine hydrochloride (2.40 g, 34.6 mmol) was added to a stirred solution of deca-1,9-diyn-5-one **32** (2.56 g, 17.3 mmol) in pyridine–ethanol (1:1; 20 cm^3) at 20 °C. After 15 min, the solution was poured into aq. hydrochloric acid (2 mol dm^{-3}; 75 cm^3) and the mixture was extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (4:1) to give the *oxime* **33**, an approximately 1:1 mixture of *E* and *Z* oximes, as a white gum (2.0 g, 71%), R_f 0.40, ether–hexane (1:1) (Found: C, 73.6; H, 8.2; N, 8.3. $C_{10}H_{13}NO$ requires C, 73.6; H, 8.0; N, 8.6%); ν_{max}(CCl_4)/cm^{-1} 3610m (O–H), 3310s (sp C–H), 3300brs (O–H), 2120m (C≡C) and 1650w (C=N); δ_H(250 MHz; $CDCl_3$) 2.65–2.36 (6 H, m), 2.24 (2 H, td, *J* 7.1 and 2.5, $CH_2CH_2CH_2C{=}N$), 1.99–1.96 (2 H, m, C≡CH) and 1.76 (2 H, quintet, *J* 7.3, $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 159.2 (s), 159.0 (s), 83.6 (s), 83.2 (s), 83.12 (s), 69.1 (d), 69.0 (d), 33.5 (t), 33.2 (t), 27.1 (t), 24.7 (t), 24.4 (t), 18.6 (t), 18.0 (t), 15.5 (t) and 14.8 (t); *m/z* (EI) 134 (12%), 124 (22), 118 (13), 111 (100), 106 (19), 94 (32), 91 (32), 79 (70), 77 (37), 67 (51), 65 (34) and 53 (66); *m/z* (CI) 164 (MH^+, 100%) and 148 (37). [Found: MH^+ 164.1075 (CI). $C_{10}H_{13}NO$ requires *M*H 164.1075].

2-(*But*-3-*ynyl*)-6-*methyl*-2,3,4,5-*tetrahydropyridine* 1-*Oxide* **35**.—Hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise to a stirred solution of the oxime **33** (150 mg, 0.92 mmol), sodium cyanoboranuide (116 mg, 1.84 mmol) and Methyl Orange solution (1 drop) in methanol (5 cm^3) at −10 °C under nitrogen, so as to just keep the solution pink. After 30 min, the solution was basified with 20% aq. sodium hydroxide, the suspension was poured into brine (20 cm^3) containing ice, and the suspension was extracted with dichloromethane (4 × 20 cm^3). The combined organic extracts were stirred in the presence of anhydrous sodium sulfate for 1 h. The solution was then filtered and the solvent was removed under reduced pressure. The compound was purified by flash chromatography on a short silica column, eluting with ethyl acetate followed by ethyl acetate–methanol (17:3) to give the *nitrone* **35** as a low melting point white solid (140 mg, 92%), R_f 0.05, ethyl acetate–methanol (9:1); ν_{max}(CCl_4)/cm^{-1} 3310s (sp C–H), 2210w (C≡C) and 1600m (C=N$^+$); δ_H(400 MHz; C_6D_6) 3.67–3.58 (1 H, m, CHN^+), 2.49–2.36 (1 H, m, $CHHCH_2C{\equiv}C$), 2.35–2.10 (2 H, m, $CH_2C{\equiv}C$), 1.88 (3 H, br s, Me), 1.84 (1 H, t, *J* 2.5, C≡CH), 1.64-

1.55 (3 H, m, CH*H*CH_2C≡C and CH_2C=N^+), 1.36–1.25 (1 H, m, $CH_2CH_2CHHCHN^+$), 1.24–1.13 (1 H, m, CH_2CH_2-CH*H*CHN^+), 1.06–0.96 (1 H, m, CH_2CHHCH_2) and 0.94–0.84 (1 H, m, CH_2CHHCH_2); δ_C(100 MHz; $CDCl_3$) 145.7 (s), 83.1 (s), 69.1 (d), 65.6 (d), 31.4 (t), 30.7 (t), 27.2 (t), 19.0 (q), 16.0 (t) and 15.9 (t); *m/z* (EI) 165 (M^+, 30%), 148 (14), 136 (13), 113 (38), 96 (100), 91 (32), 86 (33), 84 (49), 55 and (95); *m/z* (CI) 182 [$(M + NH_4)^+$, 23%] and 166 (MH^+, 100). [Found: MH^+ 166.1232 (CI). $C_{10}H_{15}NO$ requires *M*H 166.1232].

5-(*Trimethylsilyl*)*pent*-4-*ynal Oxime* **38**.—A solution of 5-(trimethylsilyl)pent-4-yn-1-ol **37**[53] (1.00 g, 6.41 mmol) in dry dichloromethane (10 cm^3) was added to a stirred suspension of PCC (1.94 g, 9.62 mmol) and powdered, activated 3 Å molecular sieves (200 mg) in dry dichloromethane (5 cm^3) at 0 °C under nitrogen. After 8 h, the suspension was filtered through a Florisil column, eluting with ether. The solvent was evaporated under reduced pressure, the residue was dissolved in ethanol–water (8 : 1; 10 cm^3) and hydroxylamine hydrochloride (450 mg, 6.41 mmol) was added. After 30 min, the solution was poured into brine (50 cm^3) and the mixture was extracted with dichloromethane (3 × 50 cm^3). The organic layers were then combined and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography to give the *oxime* **38**, a mixture of *E* and *Z* oximes, as a pale yellow gum (420 mg, 39%), R_f 0.35 and 0.40, ether–hexane (1 : 1) (Found: C, 56.8; H, 9.0; N, 8.1. $C_8H_{15}NOSi$ requires C, 56.8; H, 8.9; N, 8.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610m (O–H), 3300brm (O–H) and 2180s (C≡C); δ_H(250 MHz; $CDCl_3$) 7.51–7.47 and 6.85 (1 H, m and t, *J* 5.4, CH=N), 2.63–2.55 and 2.44–2.38 (4 H, 2 m) and 0.14 (9 H, s, Me_3Si); δ_C(100 MHz; $CDCl_3$) 150.7 (d), 150.3 (d), 105.2 (s), 104.9 (s), 86.0 (s), 85.9 (s), 28.7 (t), 24.2 (t), 17.5 (t), 16.7 (t) and 0.0 (q); *m/z* (EI) 154 (28%), 136 (33), 109 (21), 96 (10), 83 (14) and 73 (100); *m/z* (CI) 170 [MH^+, 100%], 154 (42), 90 (27) and 73 (12) [Found: MH^+ 170.1001 (CI). $C_8H_{15}NOSi$ requires *M*H 170.100].

2-*Methyl*-4,5-*dihydro*-3H-*pyrrole* 1-*Oxide* **40**.[54]—Hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise to a stirred solution of the oxime **38** (100 mg, 0.59 mmol), sodium cyanoboranuide (74 mg, 1.2 mmol) and Methyl Orange indicator solution (2 drops) in methanol (5 cm^3) at −10 °C under nitrogen, so as to just keep the solution pink. After 5 min, the solution was basified with conc. aq. ammonia, the suspension was poured into brine (20 cm^3) containing ice and then extracted with dichloromethane (4 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Benzene (20 cm^3) was added and the solution was refluxed for 16 h under nitrogen. After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on a short silica column, eluting with dichloromethane–methanol (9 : 1) to give the *nitrone* **40** as a pale yellow oil (25 mg, 43%), R_f 0.05, ethyl acetate–methanol (9 : 1); $\nu_{max}(CCl_4)/cm^{-1}$ 1610s (C=N^+), 1270s and 1230vs; δ_H(250 MHz; $CDCl_3$) 4.05–3.97 (2 H, m, CH_2N^+), 2.79–2.68 (2 H, m, $CH_2C=N^+$), 2.16–2.03 (2 H, m, $CH_2CH_2CH_2$) and 2.04 (3 H, t, *J* 1.6, Me); δ_C(100 MHz; $CDCl_3$) 144.9, 61.9, 33.0, 16.5 and 12.6; *m/z* (EI) 99 (M^+, 66%), 98 (26), 69 (15), 55 (11), 41 (100), 84 (3) and 83 (2).

2-*Methyl*-7-(*trimethylsilyl*)*hept*-6-*ynal Oxime* **44**.—Butyllithium (1.64 mol dm^{-3} in hexane; 84 cm^3, 138 mmol) was added dropwise to a stirred solution of dry diisopropylamine (19.4 cm^3, 138 mmol) in dry THF (350 cm^3) at 0 °C under nitrogen. After 10 min, propionaldehyde dimethylhydrazone[21,55] (16.9 g, 169 mmol) was added dropwise at 0 °C under nitrogen. A pale yellow precipitate formed slowly. After 1 h, 5-bromo-1-(trimethylsilyl)pent-1-yne **43**[56] (20.2 g, 92.0 mmol) was added dropwise at 0 °C under nitrogen. The precipitate slowly redissolved. After 30 min, the reaction was quenched with water (150 cm^3) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 150 cm^3) and the combined organic layers were then dried ($MgSO_4$). After removal of the solvent under reduced pressure, pyridine–ethanol (1 : 1; 100 cm^3) and hydroxylamine hydrochloride (19.2 g, 276 mmol) were added and the solution was stirred for 1 h at 20 °C. The solution was poured into hydrochloric acid (2 mol dm^{-3}; 600 cm^3) and the mixture was extracted with dichloromethane (3 × 250 cm^3). The combined organic layers were then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (85 : 15) to give the *oxime* **44**, a mixture of *E* and *Z* oximes, as a pale yellow oil (13.5 g, 69% from the bromide **43**), R_f 0.35 and 0.45, hexane–ether (1 : 1) (Found: C, 62.3; H, 10.1; N, 6.5. $C_{11}H_{23}NOSi$ requires C, 62.5; H, 10.0; N, 6.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610s (O–H), 3300brm (O–H) and 2180s (C≡C); δ_H(250 MHz; $CDCl_3$) 7.28 and 6.52 (1 H, d, *J* 7.0 and d, *J* 7.7, CH=N), 2.41–2.32 and 2.56–2.19 (3 H, m and m), 1.58–1.48 (4 H, m), 1.08 and 1.05 (3 H, d, *J* 6.8 and d, *J* 6.8, *Me*CH), 0.13 (9 H, s, Me_3Si); δ_C(100 MHz; $CDCl_3$) 157.1 (d), 156.2 (d), 107.0 (s), 106.9 (s), 84.8 (s), 34.0 (d), 33.60 (t), 29.1 (d), 26.3 (t), 26.0 (t), 19.7 (t), 18.0 (q), 17.5 (q) and 0.1 (q); *m/z* (CI) 212 (MH^+, 100%), 196 (20) and 90 (28). [Found: MH^+ 212.1471 (CI). $C_{11}H_{21}NOSi$ requires *M*H 212.1471].

2-*Methylhept*-6-*ynal Oxime* **45**.—Tetrabutylammonium fluoride (1.0 mol dm^{-3} in THF; 70 mmol) was added to a stirred solution of the oxime **44** (13.5 g, 64 mmol) in THF (275 cm^3). After 1 h, the solution was poured into sat. aq. sodium hydrogen carbonate (500 cm^3) and the layers separated. The aqueous layer was extracted with ether (2 × 250 cm^3), the combined organic layers dried ($MgSO_4$) and the solvent was removed under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ether (8 : 2) to give the *oxime* **45**, a mixture of *E* and *Z* oximes, as a pale yellow oil (8.46 g, 95%), R_f 0.30 and 0.35, hexane–ether (1 : 1) (Found: C, 69.1; H, 9.6; N, 10.1. $C_8H_{13}NO$ requires C, 69.0; H, 9.4; N, 10.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610s (O–H), 3310s (sp C–H), 3300brm (O–H), 2120m (C≡C) and 1650w (C=N); δ_H(250 MHz; $CDCl_3$) 7.27 and 6.49 (d, *J* 7.0 and d, *J* 7.7, CH=N), 3.14 and 2.43–2.33 (septet, *J* 6.9 and m, C*H*CH=N), 2.23–2.15 (2 H, m, CH_2C≡C), 1.94 (1 H, t, *J* 2.6, C≡CH), 1.61–1.43 (6 H, m) and 1.08 and 1.04 (d, *J* 6.9 and d, *J* 6.9, Me); δ_C(100 MHz; $CDCl_3$) 156.8 (d), 156.0 (d), 84.2 (s), 84.0 (s), 66.6 (d), 68.5 (d), 34.0 (d), 33.6 (t), 33.5 (t), 29.0 (d), 26.1 (t), 25.8 (t), 18.3 (t), 18.0 (q) and 17.5 (q); *m/z* (EI) 139 (M^+, 23%), 110 (12), 94 (20), 79 (43), 73 (77), 67 (49) and 55 (77); *m/z* (CI) 140 (MH^+, 100%) and 124 (26) [Found: M^+ 139.0997 (EI). $C_8H_{13}NO$ requires *M* 139.0997].

3,7-*Dimethyl*-3,4,5,6-*tetrahydro*-2H-*azepine* 1-*Oxide* **48**.—Hydrochloric acid (6 mol dm^{-3} in methanol) was added dropwise to a stirred solution of the oxime **45** (4.00 g, 28.8 mmol), sodium cyanoboranuide (3.62 mg, 57.6 mmol) and Methyl Orange solution (10 drops) in methanol (100 cm^3) at −10 °C, so as to just keep the solution pink. After 5 min, the solution was basified with 20% aq. sodium hydroxide, the suspension poured into brine (100 cm^3) containing ice and then extracted with dichloromethane (4 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Toluene (500 cm^3) was added and the solution was heated at reflux under nitrogen for 1 h. After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with dichloromethane–methanol (19 : 1) to give the *nitrone* **48** as a pale yellow oil (3.30 mg, 81%), R_f 0.30,

dichloromethane–methanol (9:1); $\nu_{max}(CCl_4)/cm^{-1}$ 1590m (C=N$^+$); δ_H(250 MHz; $CDCl_3$) 4.01 (1 H, dd, *J* 13.4 and 9.3, C*H*HN$^+$), 3.87 (1 H, d, *J* 13.4, CH*H*N$^+$), 2.43 (2 H, t, *J* 4.7, CH_2C=N$^+$), 2.12 (3 H, s, MeC=N$^+$), 1.97–1.86 (2 H, m), 1.81–1.70 (1 H, m), 1.46–1.20 (2 H, m) and 0.96 (3 H, d, *J* 6.8, *Me*CH); δ_C(100 MHz; $CDCl_3$) 148.5 (s), 70.5 (t), 38.2 (t), 33.2 (t), 30.0 (d), 22.7 (t) and 19.9 (q); *m/z* (EI) 141 (M$^+$, 35%), 124 (36), 110 (25), 98 (34), 81 (59), 69 (25), 55 (73) and 41 (100); *m/z* (CI) 142 (MH$^+$, 100%) and 126 (35) [Found: M$^+$ 141.1154 (EI). $C_8H_{15}NO$ requires *M* 141.1154].

(2R*,6S*)-1-*Hydroxy*-2,6-*dimethyl*-2-*vinylazepane* **52**.—Vinylmagnesium bromide (1.0 mol dm^{-3} in THF; 25 cm^3, 25 mmol) was added dropwise at −78 °C under nitrogen to a stirred solution of the nitrone **48** (1.76 g, 12.5 mmol) in dry THF (50 cm^3). After 1 h, the suspension was allowed to warm to 20 °C, during which time the white precipitate dissolved. Sat. aq. ammonium chloride (50 cm^3) was added and the mixture was stirred for 10 min, after which the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 cm^3). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The compound was purified by flash chromatography on silica, eluting with pentane–ether (4:1) to give the *hydroxylamine* **52** as a white solid (1.711 g, 81%), m.p. 44–46 °C (no suitable solvent for recrystallisation could be found); R_f 0.20, hexane–ether (4:1) (Found: C, 70.9; H, 11.3; N, 8.0. $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.3%); $\nu_{max}(CCl_4)/cm^{-1}$ 3590m (O–H), 3220brm (O–H), 3080m (sp^2 C–H) and 1630w (C=C); δ_H(400 MHz; $CDCl_3$) 6.24 (1 H, dd, *J* 17.7 and 11.1, C*H*=CH_2), 5.22 (1 H, dd, *J* 11.1 and 1.2, CH=C*H*H *cis* to H), 5.16 (1 H, d, *J* 17.7 and 1.2, CH=CH*H trans* to H), 3.0 (1 H, dd, *J* 13.8 and 10.4, C*H*HN), 2.94 (1 H, dd, *J* 13.8 and 2.2, CH*H*N), 2.07–2.00 (1 H, m, MeC*H*), 1.77–1.67 (2 H, m), 1.60–1.48 (4 H, m), 1.33 (3 H, s, MeCN) and 0.86 (3 H, d, *J* 6.8, *Me*CH); δ_C(100 MHz; $CDCl_3$) 140.8 (d), 114.4 (t), 64.6 (s), 62.7 (t), 38.5 (t), 37.6 (t), 32.9 (d), 24.3 (q), 20.3 (t) and 20.1 (q); *m/z* (CI) 170 (MH$^+$, 100%), 152 (100), 142 (15), 126 (11), 98 (21), 82 (25) and 68 (13) [Found: MH$^+$ 170.1545 (CI). $C_{10}H_{19}NO$ requires *M*H, 170.1545].

(2R*,6S*)-1-(4-*Methylphenylsulfonyl*)-2,6-*dimethyl*-2-*vinylazepane* **54**.—A 13% solution of titanium trichloride in dilute hydrochloric acid was added dropwise to a stirred solution of the hydroxylamine **52** (50 mg, 0.30 mmol) in THF (1 cm^3) until the purple colour persisted. The solution was poured into sat. aq. sodium hydrogen carbonate (20 cm^3) and the suspension was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried, and most of the solvent was evaporated under reduced pressure. (No attempt was made to isolate the amine **53**). Triethylamine (1 cm^3), 4-methylbenzenesulfonyl chloride (113 mg, 0.59 mmol) and DMAP (5 mg, cat.) were added and the solution was stirred at 20 °C for 56 h. The solution was poured into sat. aq. sodium hydrogen carbonate solution (20 cm^3) and the mixture was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The compound was purified by preparative TLC on silica, eluting with ether–pentane (1:1), followed by recrystallisation from light petroleum (b.p. 60–80 °C) to give the *sulfonamide* **54** as colourless crystals (47 mg, 52%), m.p. 59–60 °C; R_f 0.25, dichloromethane–methanol (9:1) (Found: C, 66.2; H, 8.1; N, 4.8. $C_{17}H_{25}NO_2S$ requires C, 66.4; H, 8.2; N, 4.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 1640w (C=C), 1600m (aromatic C=C), 1340vs (S=O) and 1160vs (S=O); δ_H(270 MHz; $CDCl_3$) 7.75 (2 H, d, *J* 8.4, $CHCSO_2$), 7.28 (2 H, d, *J* 8.4, C*H*CHCSO$_2$), 5.86 (1 H, dd, *J* 17.4 and 10.9, C*H*=CH_2), 5.07 (1 H, *J* 17.4 and 0.8, CH=C*H*H *trans* to H), 4.97 (1 H, dd, *J* 10.9 and 0.8, CH=CH*H cis* to H), 3.67 (1 H, d, *J* 15.3, C*H*HN), 2.89 (1 H, dd, *J* 15.3 and 9.5, CH*H*N), 2.43 (3 H, s, Me on aromatic ring), 1.87–1.61 (6 H, m), 1.58 (3 H, s, MeCN), 1.02–0.96 (1 H, m) and 0.85 (3 H, d, *J* 6.7, *Me*CH); δ_C(67.8 MHz; $CDCl_3$) 143.4 (d), 142.6 (s), 140.3 (s), 129.5 (d), 127.5 (d), 112.1 (t), 64.1 (s), 52.0 (t), 43.4 (t), 37.5 (t), 35.9 (d), 26.3 (q), 21.6 (q), 21.5 (t) and 19.8 (q); *m/z* (EI) 308 (MH$^+$, 12%), 292 (20), 155 (37), 152 (77), 136 (20), 106 (17), 95 (24), 91 (100), 82 (33), 68 (45), 55 (59) and 41 (56); *m/z* (CI) 308 [MH$^+$, 100%], 152 (36) and 137 (17). [Found: M$^+$ 307.1606 (EI). $C_{17}H_{25}NO_2S$ requires *M* 307.1606].

(2R*,6S*)-1-(4-tert-*Butoxycarbonyl*)-2,6-*dimethyl*-2-*vinylazepane* **55**.—A 15% solution of titanium trichloride in dilute hydrochloric acid was added dropwise to a stirred solution of the hydroxylamine **52** in THF (115 cm^3) until the solution remained purple. The solution was basified with 20% aq. sodium hydroxide and di-*tert*-butyldicarbonate (7.46 g, 34.2 mmol) was added. The suspension was stirred for 16 h at 20 °C. Sat. aq. ammonia (50 cm^3) was added and after 30 min, the layers were separated and the aqueous layer was extracted with ether (2 × 150 cm^3). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The compound was purified by flash chromatography on silica, eluting with hexane–ether (9:1) to give the *urethane* **55** as a colourless oil (3.95 g, 91%), R_f 0.40, hexane–ether (9:1) (Found: C, 71.1; H, 10.9; N, 5.4. $C_{15}H_{27}NO_2$ requires C, 71.1; H, 10.7; N, 5.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (sp^2 C–H) and 1670s (C=O); δ_H(250 MHz; $CDCl_3$) 5.96 (1 H, dd, *J* 17.3 and 10.8, C*H*=CH_2), 4.91 (1 H, d, *J* 10.8, CH=C*H*H *cis* to H), 4.88 (1 H, d, *J* 17.3, CH*H trans* to H), 3.45 (1 H, d, *J* 14.5, C*H*HN), 3.06 (1 H, dd, *J* 14.5 and 8.1, CH*H*N), 1.78–1.56 (6 H, m), 1.52 (3 H, s, MeCN), 1.42 (9 H, s, Me_3C), 1.10–1.02 (1 H, m) and 0.89 (3 H, d, *J* 6.8, MeCH); δ_C(100 MHz; $CDCl_3$) 145.2 (br d), 109.9 (t), 79.2 (br s), 61.3 (s), 50.3 (t), 43.4 (br t), 37.1 (t), 35.2 (d), 28.5 (q), 25.7 (br q), 21.4 (t) and 19.1 (q); *m/z* (CI) 198 (100%), 154 (78) and 126 (17) [Found: MH$^+$ 254.2120 (CI). $C_{15}H_{27}NO_2$ requires *M*H 254.2120].

tert-*Butyl* 2,6,9-*Trimethylundec*-6-*enylcarbamate* **56**.—*sec*-Butyllithium (1.37 mol dm^{-3} in cyclohexane; 0.23 cm^3, 0.31 mmol) was added dropwise to a stirred solution of the urethane **55** (71 mg, 0.28 mmol) and TMEDA (0.05 cm^3, 0.31 mmol) in dry ether (1 cm^3) at −78 °C under nitrogen. The solution was allowed to warm to −22 °C. Additional *sec*-butyllithium (1.37 mol dm^{-3} in cyclohexane; 0.23 cm^3, 0.31 mmol) was added. After 2 h, the reaction was quenched with water and allowed to warm to 20 °C. The solution was poured into brine (20 cm^3) and the mixture was extracted with ether (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and, after removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (19:1) to give the *carbamate* **56**, a mixture of stereoisomers, as a colourless oil (75 mg, 86%), R_f 0.35, hexane–ether (9:1) (Found: C, 73.1; H, 12.0; N, 4.5. $C_{19}H_{37}NO_2$ requires C, 73.3; H, 12.0; N, 4.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 3480m (N–H) and 1720s (C=O); δ_H(400 MHz; $CDCl_3$) 5.11 (1 H, t, *J* 7.2, CH=C), 3.07–3.02 (1 H, m, CHN), 2.92–2.86 (1 H, m, CH*H*N), 1.98–1.91 (4 H, m, CH_2C=C), 1.81–1.70 (1 H, m, C*H*CH$_2$N), 1.66 and 1.51 (3 H, 2 s, *Me*C=CH), 1.42 (9 H, s, Me_3C), 1.70–1.24 (5 H, m), 1.15–1.02 (2 H, m, $CH_2CH_2CH_2$) and 0.88–0.82 (9 H, m, *Me*CH and *Me*CH$_2$); δ_C(100 MHz; $CDCl_3$) 156.1 (s), 135.5 (s), 135.3 (s), 124.2 (d), 123.6 (d), 78.9 (s), 46.6 (t), 40.0 (t), 35.4 (d), 35.4 (d), 34.9 (t), 34.7 (t), 34.2 (t), 33.8 (t), 33.6 (d), 31.9 (t), 29.2 (t), 28.4 (q), 25.2 (t), 23.4 (q), 19.2 (q), 19.1 (q), 17.6 (q), 17.5 (q), 15.9 (q) and 11.6 (q); *m/z* (FAB) 312 (MH$^+$, 5%), 310 (6), 256 (100) and 212 (71).

(1R*,6S*,9aS*)-1-*Bromomethyl*-6,9a-*dimethylhexahydrooxazolo*[3,4-a]*azepin*-3-*one* **58**.—Bromine (1.0 mol dm^{-3} in carbon tetrachloride; 3.6 cm^3, 3.6 mmol) was added dropwise to a stirred solution of the urethane **55** (835 mg, 3.3 mmol) in carbon tetrachloride (17 cm^3) at −15 °C under nitrogen. The suspension was warmed to 20 °C, sat. aq. sodium hydrogen carbonate (5 cm^3) and aq. sodium sulfite (2 mol dm^{-3}; 5 cm^3) were added and the mixture was stirred vigorously for 10 min. The mixture was then poured into sat. aq. sodium hydrogen carbonate (50 cm^3) and was extracted with dichloromethane (3 × 50 cm^3) and the combined organic layers were dried (Na_2SO_4). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with pentane–ethyl acetate (3:2) to give the *oxazolidinone* **58** as a white solid (790 mg, 87%), m.p. 128–130 °C (from hexane); R_f 0.35, dichloromethane–ethyl acetate (19:1) (Found: C, 47.8; H, 6.5; N, 5.2. $C_{11}H_{18}BrNO_2$ requires C, 47.8; H, 6.6; N, 5.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750s (C=O); δ_H(270 MHz; $CDCl_3$) 4.35 (1 H, t, *J* 6.7), 3.62–3.55 (1 H, m, C*H*HN), 3.55 (1 H, dd, *J* 11.0 and 7.1, C*H*HBr), 3.43 (1 H, dd, *J* 11.0 and 6.4, CH*H*Br), 2.96 (1 H, dd, *J* 14.4 and 2.9, CH*H*N), 2.13 (1 H, dd, *J* 14.6 and 7.0), 2.07–1.97 (1 H, m, *Me*CH), 1.83–1.43 (5 H, m), 1.20 (3 H, s, *Me*CN) and 0.99 (3 H, d, *J* 7.0, *Me*CH); δ_C(67.5 MHz; $CDCl_3$) 156.4 (s), 79.8 (d), 63.3 (s), 45.3 (t), 39.6 (t), 36.8 (t), 31.9 (d), 26.8 (t), 18.9 (q), 18.6 (t) and 17.4 (q); *m/z* (EI) 278 [MH^+ (^{81}Br), 17%], 276 [MH^+ (^{79}Br), 19], 262 (42), 260 (46), 234 (17), 232 (18), 207 (19), 205 (20), 196 (40), 194 (27), 192 (29), 152 (73), 136 (10), 122 (11), 110 (19), 98 (23), 84 (39), 82 (89), 69 (42), 67 (38), 55 (96) and 41 (100) [Found: MH^+ 277.0497 and 275.0532 (EI). $C_{11}H_{18}{}^{81}BrNO_2$ requires *M*H 277.0501 and $C_{11}H_{18}{}^{79}BrNO_2$ requires *M*H 275.0521].

(1R*,6S*,9aS*)-1,6,9a-*Trimethylhexahydrooxazolo*[3,4-a]-*azepin*-3-*one* **57** and (1R*,6R*,9aR*)-1-*Bromomethyl*-6,9a-*dimethylhexahydrooxazolo*[3,4-a]*azepin*-3-*one* **58**.—Bromine (1.0 mol dm^{-3} in carbon tetrachloride; 17.2 cm^3, 17.2 mmol) was added dropwise to a solution of the urethane **55** (3.95 g, 15.6 mmol) in carbon tetrachloride (100 cm^3) at −20 °C. The suspension was warmed to 20 °C, sat. aq. sodium hydrogen carbonate (50 cm^3), aq. sodium sulfite (2 mol dm^{-3}; 50 cm^3) and dichloromethane (100 cm^3) were added and the mixture was stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 cm^3). After removal of the solvent under reduced pressure, the mixture was separated by flash chromatography on silica, eluting with dichloromethane–ethyl acetate (95:5) to give the *oxazolidinone* **58** (2.78 g, 65%) and the *oxazolidinone* **57** both as white solids (430 mg, 14%), m.p. 88–90 °C (from hexane); R_f 0.15, dichloromethane–ethyl acetate (19:1) (Found: C, 66.8; H, 9.8; N, 7.0. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.71; N, 7.10%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1760s (C=O); δ_H(250 MHz; $CDCl_3$) 4.19 (1 H, dd, *J* 6.5, CHO), 3.58 (1 H, dd, *J* 14.4 and 4.0, 1.6, C*H*HN), 2.94 (1 H, dd, *J* 14.4 and 2.7, CH*H*N), 2.03–1.97 (1 H, m, C*H*CH_2N), 1.80–1.34 (6 H, m), 1.27 (3 H, d, *J* 6.5, *Me*CHO), 1.07 (3 H, s, MeCN) and 0.97 (3 H, d, *J* 7.0, *Me*CHCH_2N); δ_C(100 MHz; $CDCl_3$) 157.8 (s), 77.2 (d), 63.2 (s), 45.3 (s), 38.4 (t), 36.9 (t), 31.9 (t), 19.1 (q), 18.5 (t), 17.2 (q) and 13.0 (q); *m/z* (EI) 197 (M^+, 15%), 182 (100), 154 (15), 138 (22), 127 (31), 114 (67), 112 (51), 96 (32), 82 (39), 69 (25), 55 (61) and 41 (58); *m/z* (CI) 198 (MH^+, 100%] and 182 (28) [Found: MH^+ 198.1494 (CI). $C_{11}H_{19}NO_2$ requires *MH* 198.1494].

(1R*,6R*,9aR*)-1-*Bromomethyl*-6,9a-*dimethylhexahydrooxazolo*[3,4-a]*azepin*-3-*one* **57** *from* (1R*,6S*,9aS*)-1,6,9a-*Trimethylhexahydrooxazolo*[3,4-a]*azepin*-3-*one* **58**.—A stirred solution of the bromomethyl oxazolidinone **58** (50 mg, 0.18 mmol), AIBN (1 mg) and tributyltin hydride (0.17 cm^3, 0.63 mmol) in dry toluene (6 cm^3) was heated at reflux under nitrogen for 18 h. The solution was poured onto a silica column and elution with dichloromethane followed by dichloromethane–ethyl acetate (19:1) gave the *methyl oxazolidinone* **57** as a white solid (35 mg, 98%).

(6R*,9aR*)-1-*Bromomethyl*-6,9a-*dimethylhexahydrooxazolo*-[3,4-a]*azepine*-3,5-*dione* **59**.—The oxazolidinone **58** (2.78 g, 10.1 mmol), sodium periodate (4.30 g, 20.1 mmol) and ruthenium trichloride hydrate (100 mg, cat.) were added to a biphasic mixture of carbon tetrachloride (60 cm^3), water (60 cm^3) and acetonitrile (60 cm^3). After stirring the mixture for 24 h at 20 °C, more ruthenium trichloride hydrate (950 mg) and sodium periodate (8.6 g, 20.1 mmol) were added. The mixture was stirred for a further 48 h and then aq. sodium sulfite (2 mol dm^{-3}; 100 cm^3) was added. Dichloromethane (100 cm^3) was then added, the layers were separated and the (black) aqueous layer was extracted with dichloromethane (2 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography on silica, eluting with dichloromethane–ethyl acetate (19:1) gave the recovered starting material **58** (362 mg, 13%) and the *imide* **59** as a white solid (1.87 g, 64%), m.p. 202–206 °C (from toluene); R_f 0.20, ethyl acetate–pentane (3:1) (Found: C, 45.5; H, 5.5; N, 4.9. $C_{11}H_{10}BrNO_3$ requires C, 45.5; H, 5.6; N, 4.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1810vs (C=O) and 1700m (C=O); δ_H(270 MHz; $CDCl_3$) 4.30 (1 H, dd, *J* 7.3 and 5.9, CHO), 3.56 (1 H, dd, *J* 11.2 and 7.3, C*H*HBr), 3.45 (1 H, dd, *J* 11.2 and 5.9, CH*H*Br), 2.67–2.59 (1 H, m, C*H*Me), 2.08–1.77 (6 H, m), 1.50 (3 H, s, MeCN) and 1.21 (3 H, d, *J* 6.5, *Me*CH); δ_C(67.5 MHz; $CDCl_3$) 174.0 (s), 151.0 (s), 82.1 (d), 63.7 (7), 40.1 (d), 37.2 (t), 32.1 (t), 25.7 (t), 21.8 (t), 18.5 (q) and 17.3 (q); *m/z* (EI) 292 [MH^+ (^{81}Br), 14%], 290 [MH^+ (^{79}Br), 16], 194 (44), 192 (42), 166 (20), 150 (19), 98 (100), 95 (21), 80 (23), 69 (37), 55 (49) and 42 (54). [Found: M^+ 291.0306 and 289.0314 (EI). $C_{11}H_{10}{}^{81}BrNO_3$ requires *M* 291.0294 and $C_{11}H_{10}{}^{79}BrNO_3$ requires *M* 289.0314].

(1R*,9aR*)-1-*Bromomethyl*-6,9a-*dimethyl*-6-(*phenylselanyl*)-*hexahydrooxazolo*[3,4-a]*azepin*-3-*one* **60**.—Dibutylboron triflate (1.0 mol dm^{-3} in dichloromethane; 0.82 cm^3, 0.82 mmol) was added dropwise to a stirred solution of the oxazolidinone **59** (200 mg, 0.68 mmol) and 2,6-lutidine (104 mm^3, 0.95 mmol) in dry dichloromethane (1 cm^3) at 0 °C under nitrogen. After 1 h, a solution of benzeneselanyl chloride (144 mg, 0.74 mmol) in dry dichloromethane (1 cm^3) was added dropwise under nitrogen at 0 °C. The solution was warmed to 20 °C and quenched with sat. aq. sodium hydrogen carbonate (20 cm^3). The mixture was then extracted with dichloromethane (3 × 20 cm^3) the combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The mixture was purified by flash chromatography on silica, eluting with dichloromethane–ethyl acetate (98:2) to give the *selenides* **60**, an approximately 2:1 mixture of diastereoisomers, as a white solid (208 mg, 67%), R_f 0.50 and 0.55, dichloromethane–ethyl acetate (19:1) (Found: C, 45.6; H, 4.5; N, 3.1. $C_{17}H_{20}BrNO_3Se$ requires C, 45.9; H, 4.5; N, 3.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1790s (C=O) and 1680m (C=O); δ_H(250 MHz; $CDCl_3$) 7.77 and 7.64 (2 H, dd, *J* 8.0 and 1.3 and dd, *J* 8.0 and 1.3, CHCSe), 7.52–7.32 (3 H, m), 4.53 and 4.38 (1 H, dd, *J* 8.3 and 6.0 and dd, *J* 6.7 and 6.7, CHO), 3.69–3.59 (1 H, m, C*H*HBr), 3.54–3.42 (1 H, m, CH*H*Br) 2.37–1.50 (6 H, m) and 1.81, 1.70, 1.55 and 1.28 (6 H, 4 × s, Me); δ_C(100 MHz; $CDCl_3$) 175.4 (s), 174.6 (s), 154.4 (s), 152.7 (s), 138.7 (d), 138.1 (d), 130.0 (d), 129.7 (d), 128.1 (d), 128.9 (d), 127.2 (d), 125.7 (s), 83.8 (d), 83.7 (d), 65.4 (s), 65.0 (s), 54.3 (s), 53.5 (s), 41.4 (d), 38.2 (d), 37.6 (d), 36.5 (d), 32.5 (q), 25.9 (t), 25.8 (t), 23.6 (q), 20.4 (t), 19.9 (t), 18.1 (q) and 17.9 (q); *m/z* (EI) 447 [M^+ (^{81}Br, ^{80}Se), 53%], 445 [M^+ (^{81}Br, ^{78}Se) and

(^{79}Br, ^{80}Se), 70], 314 (29), 312 (28), 309 (18), 293 (26), 291 (28), 290 (100), 288 (79), 262 (68), 260 (68), 234 (33), 233 (19), 218 (60), 216 (61), 157 (58), 136 (28), 121 (24) and 98 (90); *m/z* (CI) 448 [MH^+ (^{81}Br, ^{80}Se), 29%], 446 [MH^+ (^{81}Br, ^{78}Se) and (^{79}Br, ^{80}Se), 42], 444 [MH^+ (^{79}Br, ^{78}Se), 18], 309 (11), 308 (17), 307 (19), 292 (71), 290 (100), 288 (26), 212 (24), 210 (46), 166 (11), 139 (12), 138 (13), 98 (40) and 78 (20) [Found: M^+ 444.979 (EI). $C_{17}H_{20}{}^{79}BrNO_3{}^{80}Se$ requires M^+ 444.979].

(1R*,9aS*)-1-*Bromomethyl*-6,9a-*dimethyl*-5,8,9,9a-*tetrahydro*-1H,3H-*oxazolo*[3,4-a]*azepine*-3,5-*dione* **61**.—Sodium hydrogen carbonate (43 mg, 0.52 mmol) and sodium periodate (302 mg, 1.41 mmol) were added to a stirred solution of the mixture of the selenides **60** (208 mg, 0.47 mmol) in ethanol (21 cm^3), dichloromethane (12 cm^3) and water (3 cm^3) at −20 °C. After 2 h, the solution was allowed to warm to 0 °C and stirred for 12 h at that temp. The white suspension was poured into sat. aq. sodium hydrogen carbonate (50 cm^3) and the mixture was extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and, after removal of the solvent under reduced pressure, the crude mixture of α,β-unsaturated imides was filtered through a short silica plug, eluting with dichloromethane followed by dichloromethane–ethyl acetate (95:5). The *endo*:*exo* ratio was 1.5:1 by ^{1}H NMR (90 MHz; $CDCl_3$). The crude mixture of compounds was dissolved in dichloromethane–methanol (1:1; 8 cm^3) containing a few drops of water and then triphenylphosphine (49 mg, 0.19 mmol) was added. The stirred solution was heated at reflux under nitrogen for 24 h. After cooling, the solution was poured into brine (20 cm^3) and the mixture was extracted with dichloromethane (3 × 20 cm^3). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with dichloromethane–ethyl acetate (95:5) to give the *imide* **61** as a white solid (47 mg, 35%), by ^{1}H NMR (250 MHz; $CDCl_3$), a 23:1 mixture of endocyclic and exocyclic isomers. Recrystallisation from ethyl acetate gave a 36:1 mixture (35 mg, 26%); m.p. 169–171 °C; R_f 0.30, dichloromethane–ethyl acetate (19:1) (Found: C, 45.6; H, 4.8; N, 4.6. $C_{11}H_{14}BrNO_3$ requires C, 45.9; H, 4.9; N, 4.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1785s (C=O) and 1660m (α,β-unsaturated imide); δ_H(250 MHz; $CDCl_3$) 6.36 (1 H, t, *J* 4.8, CH=CC=O), 4.36 (1 H, t, *J* 6.8, CHO), 3.56 (dd, *J* 11.2 and 6.8, C*H*HBr), 3.45 (1 H, dd, *J* 11.2 and 6.8, CH*H*Br), 2.56–2.48 (2 H, m, CH_2CH=C), 2.23 (1 H, dt, *J* 14.7 and 5.0, C*H*HCH$_2$C=C), 2.11 (1 H, ddd, *J* 14.7, 10.6 and 5.0), CH*H*CH$_2$C=C), 2.01 (3 H, dd, *J* 3.1 and 1.6, *Me*C=CH) and 1.36 (3 H, s, MeCN), exocyclic isomer **62** 5.88 (1 H, d, *J* 1.2, C=C*H*H) and 5.50 (1 H, br s, C=CH*H*); δ_C(100 MHz; $CDCl_3$) 165.6 (s), 151.0 (s), 137.8 (d), 131.7 (s), 81.3 (d), 62.6 (s), 36.0 (t), 25.9 (t), 25.6 (t), 22.7 (q) and 16.8 (q); *m/z* (CI) 307 [$(M + NH_4)^+$ (^{81}Br), 18%], 305 [$(M + NH_4)^+$ (^{79}Br), 16], 290 [MH^+ (^{81}Br), 100], 288 [MH^+ (^{79}Br), 95], 227 (21), 210 (87) and 166 (18) [Found: MH^+ 288.0235 (CI). $C_{11}H_{14}{}^{79}BrNO_3$ requires *M*H 288.0235].

3,7-*Dimethyl*-7-*vinyl*-2,5,6,7-*tetrahydro*-1H-*azepin*-2-*one* **49**.—Activated zinc dust (28 mg, 0.44 mmol) was added to a stirred suspension of the oxazolidinone **61** (36:1 *endo*:*exo*; 35 mg, 0.12 mmol) in a saturated solution of ammonium chloride in methanol–water (4:1; 2 cm^3). After 15 min, the suspension was poured into sat. aq. sodium hydrogen carbonate (20 cm^3) and the mixture was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with dichloromethane–ethyl acetate (4:1) to give the (±)-*lactam* **49** as a white solid (13 mg, 88%), m.p. (ex HPLC) 53–54 °C; R_f 0.20, 19:1 dichloromethane–ethyl acetate and 0.7, ethyl acetate–methanol–ammonia (150:9:1) (Found: C, 72.9; H, 9.4; N, 8.3. $C_{10}H_{15}NO$ requires C, 72.7; H, 9.2; N, 8.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 3400m (N–H), 1665s (α,β-unsaturated amide) and 1620s (α,β-unsaturated amide); λ_{max}(EtOH)/nm 218 (ε/dm^3 mol^{-1} cm^{-1} 15 200). δ_H(270 MHz; $CDCl_3$) 6.13 (1 H, tq, *J* 4.5 and 1.6, CH=CC=O), 5.81 (1 H, dd, *J* 17.1 and 10.4, C*H*=CH$_2$), 5.8 (1 H, br s, NH) 5.12 (1 H, dd, *J* 17.1 and 0.8, CH=CH*H* *trans* to H), 5.07 (1 H, dd, *J* 10.4 and 0.8, CH=CH*H* *cis* to H), 2.37–2.31 (2 H, m, CH_2CH=C), 1.95 (3 H, q, *J* 1.6, *Me*C=CH), 1.92–1.89 (2 H, m, CH_2CH_2CH=C) and 1.32 (3 H, s, *Me*CN); δ_H(400 MHz; C_6D_6) 7.4 (1 H, br s, NH) 5.69 (1 H, t, *J* 4.8, CH=CCO), 5.48 (1 H, dd, *J* 17.1 and 10.5, C*H*=CH$_2$), 5.07 (1 H, dd, *J* 17.1 and 0.9, CH=CH*H* *trans* to H), 4.83 (1 H, dd, *J* 10.5 and 0.9, CH=CH*H* *cis* to H), 2.14 (3 H, q, *J* 1.6, *Me*C=CH), 1.87–1.82 (2 H, m, CH_2CH=C), 1.49 (1 H, ddd, *J* 14.0, 8.6 and 6.5, C*H*HCH$_2$CH=C), 1.36 (dt, *J* 14.0 and 5.4, CH*H*CH$_2$CH=C) and 1.03 (3 H, s, MeCN); δ_C(67.8 MHz; $CDCl_3$) 170.0 (s), 142.0 (d), 136.4 (d), 130.9 (s), 113.2 (t), 56.5 (s), 38.1 (t), 30.1 (q), 27.4 (t) and 22.5 (q); δ_C(100 MHz; C_6D_6) 170.0 (s), 142.7 (d), 135.1 (d), 132.1 (s), 112.6 (t), 56.2 (s), 38.4 (t), 30.1 (q), 27.5 (t) and 23.0 (q); *m/z* (EI) 150 (17%), 137 (42), 122 (27), 110 (27), 97 (52), 70 (81), 67 (100), 53 (50) and 41 (71); *m/z* (CI) 166 (MH^+, 100%). [Found: MH^+ 166.1230 (CI). $C_{10}H_{15}NO$ requires *M*H 166.1232].

Acknowledgements

We thank the SERC for supporting this work, SmithKline Beecham Pharmaceuticals for a CASE award (MEF) and the British Council for sponsoring a collaboration with Professor G. Helmchen under the ARC Programme. We thank the Royal Society for the award of a Royal Society Leverhulme Senior Research Fellowship (ABH) and Pfizer Central Research (Sandwich) for financial support. We thank Professors I. Murakoshi and T. Sekine for supplying spectra of acacialactam and for helpful correspondence, Professor J. A. Marco for a preprint of reference 49 and Professors P. Beak and P. A. Evans for helpful discussions.

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Paper 4/02761B
Received 10*th May* 1994
Accepted 10*th August* 1994