Electrophile-mediated Cyclisations: Regioselective Synthesis of Substituted Cyclic Nitrones and Crystal Structures of the Nitrone Cycloadducts

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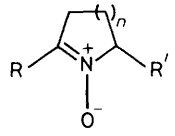
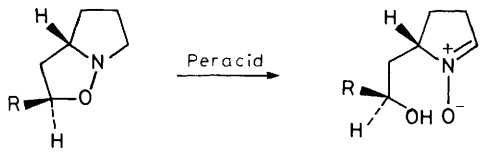
A series of allenic oximes (**2a,b**) and (**3a,b**) have been prepared and shown to undergo Ag[I] catalysed cyclization *via* nitrogen to give the isomerically defined heterocyclic nitrones (**4**), (**5**), (**7**), and (**9**). In the case of the (*E*)-γ-allenic oximes cyclisation *via* oxygen was observed leading to the corresponding dihydro-oxazines, *e.g.* (**6**). The ketoxime-derived nitrones (**4**) and (**5**) were relatively unreactive but the less hindered aldoxime derivatives (**7**) and (**9**) were readily trapped by a range of 1,3-dipolarophiles providing access to derivatives of *trans*-2,6-disubstituted piperidines and *trans*-2,5-disubstituted pyrrolidines. Crystallographic analysis of the methiodide derivatives of the cycloadducts (**8d**) and (**8e**) served to confirm these stereochemical assignments and the application of this methodology to the synthesis of the unusual pyrrolizidine alkaloid (±)-(**18**) is described. Attempts to trigger the cyclisation of allenic oximes (**2a,b**) and (**3a,b**) with mercury(II) and palladium(II) electrophiles failed. No reaction was observed between the corresponding olefinic oximes (**22a,b**) and Ag[I] and although the acetylenic derivatives (**23a,b**) did react with Ag[I] all attempts to trap a nitrone or otherwise characterise this reaction pathway failed.

Among the synthetically useful 1,3-dipoles, nitrones have found widespread use in the construction of a variety of nitrogen-containing molecular assemblies.[1] In a similar fashion the heterocyclic-based nitrones such as (**1**) provide a flexible entry



(**1**)

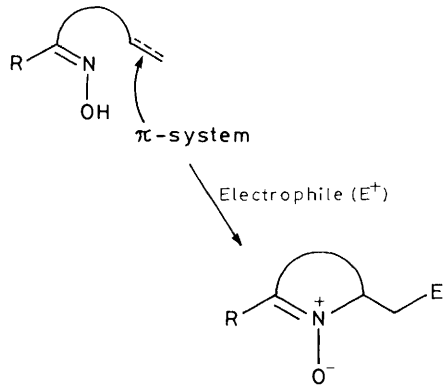
into a range of heterocyclic targets. There are, however, problems associated with the generation of these heterocyclic 1,3-dipoles. Although simple unsubstituted, or symmetrically substituted, nitrones (**1**; R=R′) are readily available by oxidation of an *N*-hydroxylamine, when this process is applied to an unsymmetrical substrate, mixtures of isomeric nitrones (**1**; R ≠ R′) are produced.† Because of this lack of regiocontrol, efforts have been made to prepare nitrones such as (**1**; R ≠ R′) in a regioselective manner and the procedures developed by LeBel and Tufariello based on the stereospecific oxidation of isoxazolines, Equation (1), are a significant advance in the field.[3]



Equation (1)

† This problem has been discussed.[1c] For some more recent preparations of nitrones *via* oxidation of an *N*-hydroxylamine see ref. 2.
‡ Nitrones have been generated by the intra- and inter-molecular reactions of oximes with electron-deficient alkenes.[4]
§ For cyclisations involving an oxonium ion species see ref. 5.

Our own interest in this area was stimulated by the possibility of devising a method that would allow the heterocyclic-based dipole to be generated from an acyclic precursor, without the necessity of a formal oxidation step. The approach that has been developed is based on the cyclization of an oxime, *via* nitrogen, to a π-bond that has been activated by an appropriate electrophile [equation (2)].[4,5]‡,§ This constitutes in net effect an



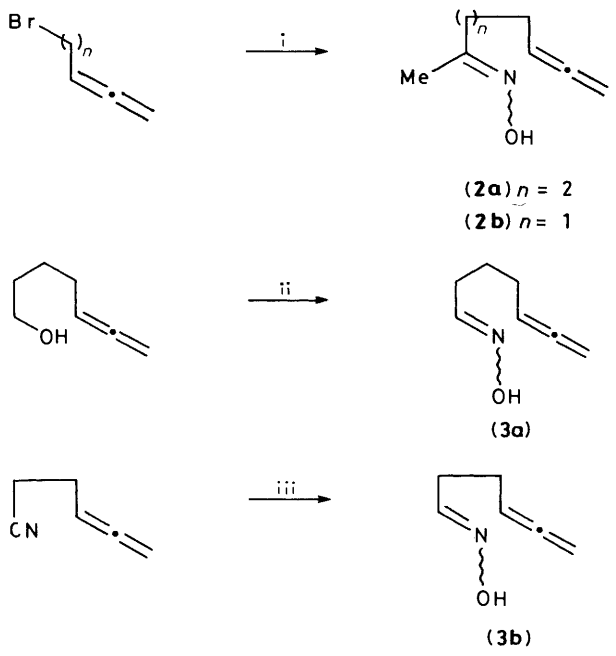
Equation (2)

intramolecular alkylation of an oxime, a process that has, in a more conventional S_N2-sense, found only limited application to nitrone synthesis.[6] In this paper we present an account of these studies and the scope and limitations of methods developed are discussed.[7]

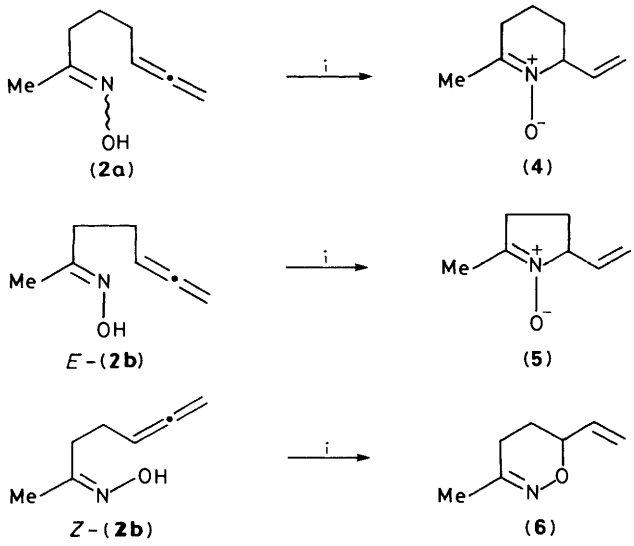
Results and Discussion

Various possibilities exist for the type of activated π-system that would participate in this cyclization sequence, but the use of an allenic moiety, activated under very mild conditions by silver(I), was especially attractive. This π-bond/electrophile combination has been very successfully used by a number of groups for the synthesis of pyrrolidines and piperidines, as well as oxygen-containing heterocycles.[8]

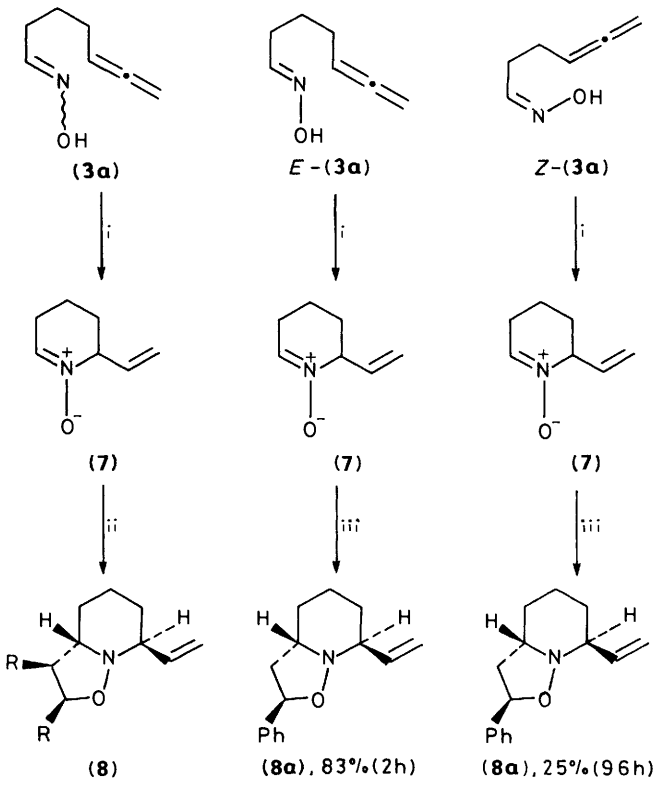
A series of γ- and δ-allenic oximes (**2a,b**) and (**3a,b**) were



Scheme 1. *Reagents:* i, acetone oxime, BuLi (2 equiv.); ii, pyridinium chlorochromate, then NH_2OH, sodium acetate; iii, Bu^i_2AlH, then NH_2OH·HCl, sodium acetate



Scheme 2. *Reagents:* i, $AgBF_4$, CH_2Cl_2



Scheme 3. *Reagents:* i, $AgBF_4$, CH_2Cl_2; ii, 1,3-dipolarophile; iii, styrene

therefore prepared using standard methodology (Scheme 1). The ketoximes (**2a**) and (**2b**) were obtained by alkylation of acetone oxime dianion[9] with the appropriate allenic electrophile. The oxime (**3a**) was obtained from the corresponding aldehyde, and the oxime (**3b**) was most efficiently prepared by reduction of hexa-4,5-dienenitrile[10] with di-isobutylaluminium hydride, followed by quenching the reaction mixture with aqueous NH_2OH·HCl/NaOAc. After purification by distillation or chromatography, all oximes were all obtained as essentially 1:1 mixtures of the corresponding *E*- and *Z*-isomers.

The cyclization of the ketoximes (**2a**) and (**2b**) using silver tetrafluoroborate in dichloromethane was rapid, and the isomerically pure nitrones (**4**) and (**5**) were isolated in 50 and 74% yields respectively (Scheme 2). Although *Z*-(**2a**) slowly underwent equilibration to the *E*-isomer, which cyclized to give (**4**) under these conditions, it was otherwise inert. This was not however true of *Z*-(**2b**) which cyclized *via* oxygen to give the oxazine (**6**) (34%). Unfortunately, despite their facile formation, the nitrones (**4**) and (**5**) both failed to react with a variety of 1,3-dipolarophiles, even under forcing conditions.

By contrast, the aldoximes (**3a**) and (**3b**) offered access to less substituted and more reactive nitrones and, using the same conditions as those described above, cyclization of *E*/*Z*-(**3a**) and *E*-(**3b**) afforded the corresponding nitrones (**7**) and (**9**) respectively. The piperinyl derivative (**7**) rapidly decomposed on attempted isolation, but was trapped *in situ* by a range of 1,3-dipolarophiles to give the cycloadducts (**8a**—**e**) in moderate yield (Scheme 3) (Table 1). The yields shown here are based on a 1:1 mixture of *E*- and *Z*-(**3a**) and a more realistic evaluation of the efficiency of these reactions was apparent when isomerically pure *E*-(**3a**) was employed. Cyclization of *E*-(**3a**) ($AgBF_4/CH_2Cl_2$) in the presence of an excess of styrene gave the cycloadduct (**8a**) in 83% yield after 2 h. When *Z*-(**3a**) was used, (**8a**) was isolated in 25% yield after 96 h, together with a substantial amount of polymeric material that is presumed to arise by oxidation of the oxime by Ag^I, a process that is competitive with *E*/*Z* isomer equilibration.

Although the pyrrolidine derivative (**9**) was somewhat more stable, this nitrone was not routinely purified but was trapped *in situ* by either styrene or but-3-en-2-one to give (**10a**), (42%) and (**10b**), (36%) respectively (Scheme 4). As with *Z*-(**2b**), *Z*-(**3b**) also underwent cyclization *via* oxygen to give the dihydroxazine (**11**), although this compound proved to be difficult to purify and characterise.

The stereochemical assignment of both series of cycloadducts was based primarily on COSY and n.O.e. difference spectroscopy. Key experiments (see Figure 1) involved irradiation of H_a which produced an enhancement of H_b and $H_{c'}$, but not of H_d and irradiation of H_d produced, where appropriate, an enhancement of H_c. Somewhat inconclusive results were obtained for the cyclohexadiene adduct (**8e**) and in order to establish

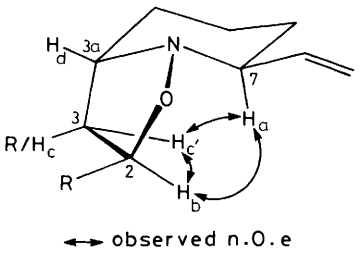
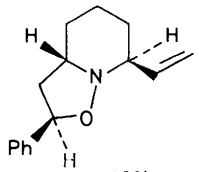
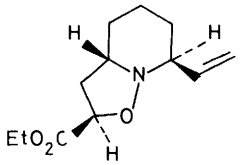
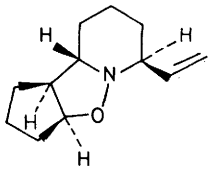
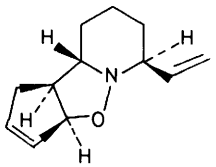
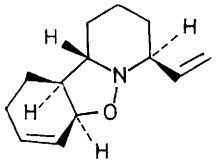


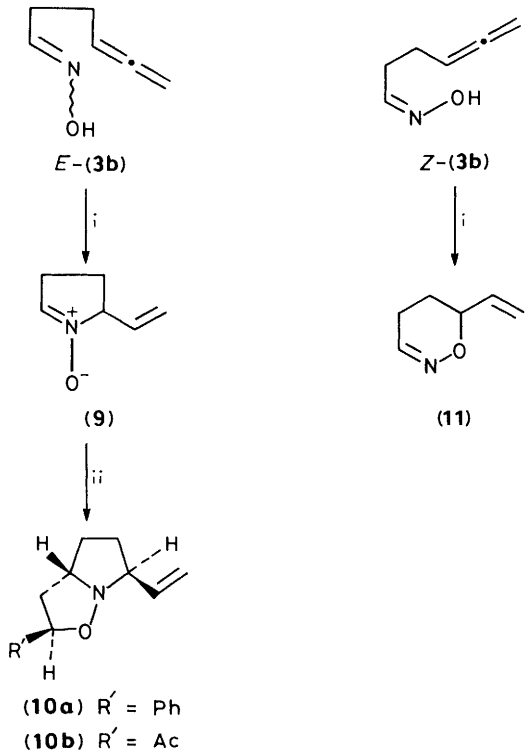
Figure 1.

Table 1.

1,3-Dipolarophile	Cycloadduct (8), % yield
Styrene	 (8a), 42%
Ethyl acrylate	 (8b), 25%
Cyclopentene	 (8c), 29%
Cyclopentadiene	 (8d), 43%
Cyclohexa-1,4-diene	 (8e), 35%

firmly the stereochemical assignments that had already been made, cycloadducts (**8d**) and (**8e**) (as their methiodide salts) were subjected to *X*-ray crystallographic analysis. The results of these studies are shown in Figure 2 and are in agreement with the ^{1}H n.m.r. assignments; this served to correct the assignment of (**8e**) that was made in an earlier publication.[7a] All cyclo-

* A synthesis of (−)-(18) has been reported, although the absolute configuration of the naturally occurring material is unknown.[13b]



Scheme 4. *Reagents:* i, $AgBF_4$, CH_2Cl_2; ii, 1,3-dipolarophile

adducts were therefore shown to have the same relative stereochemistry and this is consistent with the approach of the 1,3-dipolarophile in an *exo* fashion to the less hindered face of the 1,3-dipole.[11] We have also attempted to trigger the cyclization of oximes (**2a**—**d**) either using mercury(II) ($Hg(OAc)_2$)[8d] or palladium(II) ($PdCl_2$,CO,MeOH)[12] as the electrophilic component, but we have been uniformly unsuccessful in generating a nitrone with these systems.

Clearly the reactions shown in Schemes 3 and 4 provide a stereocontrolled entry into *trans*-2,6-disubstituted piperidines and *trans*-2,5-disubstituted pyrrolidines and we have illustrated the potential of this methodology by a synthesis of the structurally unusual pyrrolizidine alkaloid (**18**), a component of the venom of *Solenopis xenoveneum*, a variety of thief ant.[13a,*] The bicyclic structure of (**18**) contains two *trans*-2,5-disubstituted pyrrolidine ring units but we focused on setting the *trans* relationship between C-3 and C-7a of (**18**) using a 1,3-dipolar cycloaddition.

The sequence began by the synthesis of the oxime (**12**) from oct-1-yn-3-ol in four steps. Separation of the *E*- and *Z*-(**12**) was effected by chromatography and equilibration of *Z*-(**12**) was achieved by allowing a chloroform solution of this isomer to stand overnight; cyclization of *Z*-(**12**) in the presence of Ag^I was facile and the dihydroxazine (**19**) was obtained in 90% yield.

Cyclization of *E*-(**12**) with $AgBF_4$ gave the nitrone (**13**) and this species was trapped by buten-2-one to give a 1:1 mixture of epimeric adducts (**14a**,**b**) (48%). Best results were obtained if the nitrone was quickly purified by flash chromatography prior to exposure to the dipolarophile. The structures of (**14a**,**b**) were established as described above (COSY, n.O.e. difference spectroscopy) and although it is possible that (**14b**) was formed by equilibration of (**14a**) under the reaction conditions, this was not vigorously established. This was the first occasion on which epimeric adducts had been isolated, although both isomers were carried through to the final synthetic target.

The remaining stereocentre present in (**18**), that of the methyl

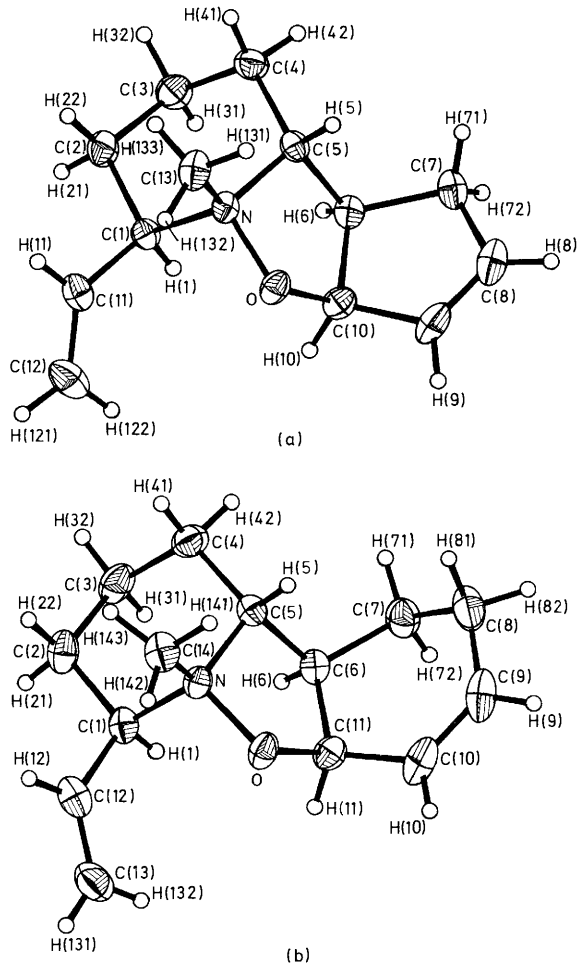
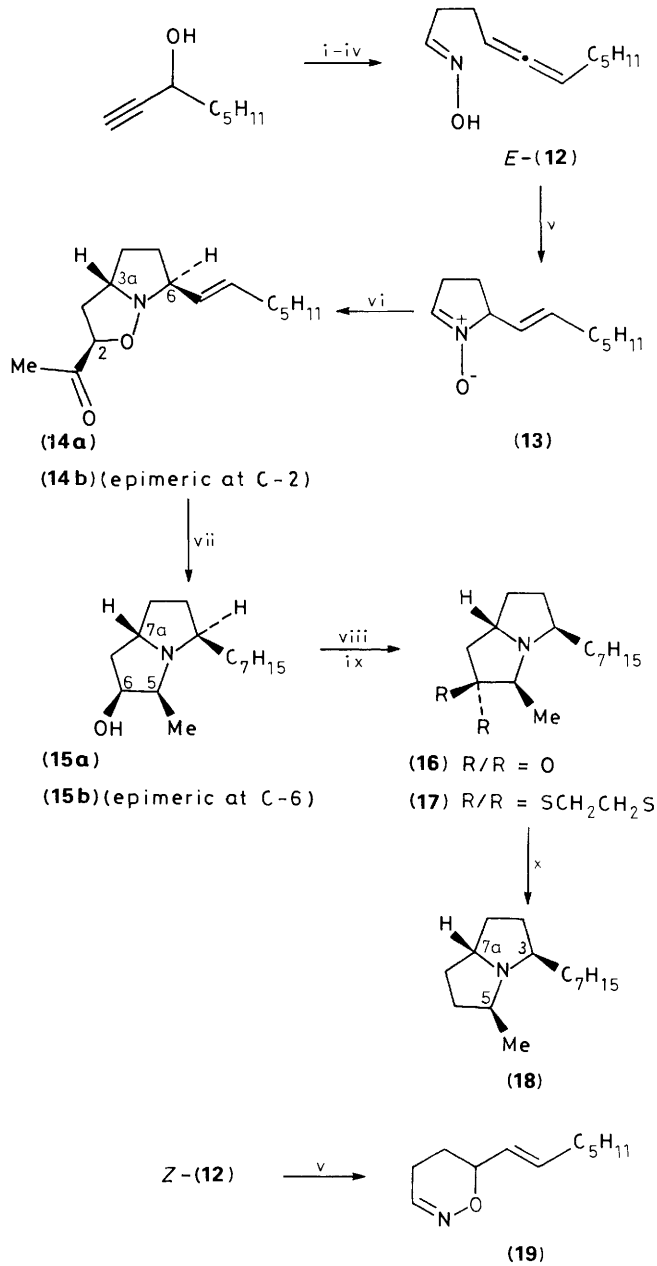


Figure 2. ORTEP diagrams for (a) (**8d**)·MeI and (b) (**8e**)·MeI

substituent at C-5 was readily established by reduction of (**14a**) and (**14b**) separately with $H_2/PdCl_2$ in ethanol. The epimeric alcohols (**15a**) and (**15b**) were both isolated in 76% yield and the stereochemistry at C-5 is presumably due to a face-selective reduction of an intermediate cyclic iminium ion.[14] To complete the synthesis of (**18**) all that remained was to affect the deoxygenation of the secondary hydroxy functions of (**15a,b**). Various methods were attempted but the lack of reactivity of (**15b**), due to the hindered environment of the hydroxy residue, undermined this approach. A more effective solution, which also served to confirm our earlier stereochemical assignments, involved oxidation of (**15a,b**) with Jones' reagent to give the unstable amino ketone (**16**) which was immediately treated with an ethane-1,2-dithiol to give a *single* dithioketal (**17**) in 48% overall yield. Completion of the synthetic sequence involved desulphurisation of (**17**) with Raney nickel to give (**18**) in 61% yield. Spectral data for (**18**) were identical with those reported earlier and a comparison was made of this synthetic material with a mixture of all four possible diastereoisomers, prepared according to the procedures described by Jones *et al.*[13]

The possibility of preparing nitrones from alkene and alkyne precursors was also considered worthy of examination.

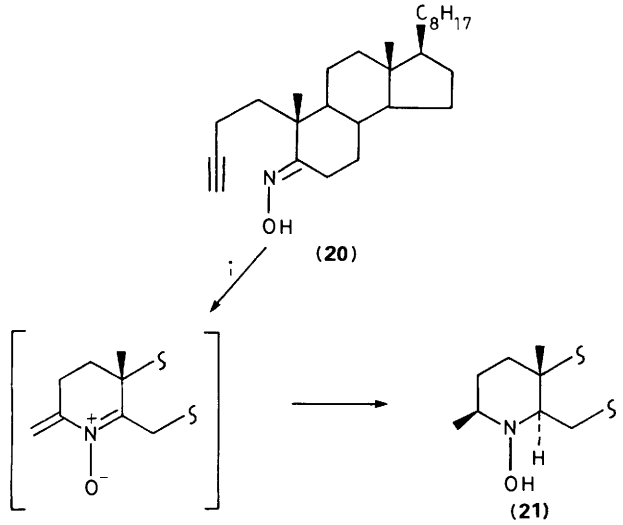
Cyclization of olefinic oximes under a number of conditions have been studied by various groups and although heterocyclic products have been obtained, the intermediacy of nitrones is not usually invoked.[15] One very interesting transformation that has been suggested to proceed *via* a nitrone involves the acetylenic oxime (**20**).[16] Reaction of this oxime with sodium borohydride in methanol gave hydroxylamine (**21**) in 90% yield and although



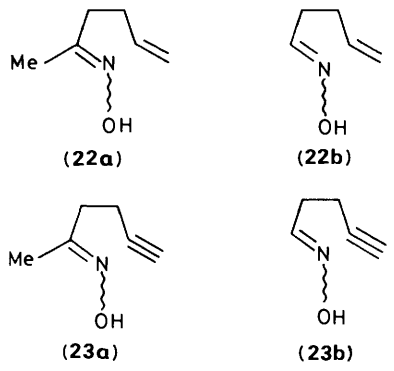
Scheme 5. *Reagents:* i, $MeC(OEt)_3$, pivalic acid, 110 °C (77%); ii, $LiAlH_4$, ether, −60 °C to 20 °C (97%); iii, *p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C, then KCN, Me_2SO, 75 °C (78%); iv, Bu^i_2AlH, ether, 20 °C, then NH_2OH·HCl, NaOAc, H_2O (76%); v, $AgBF_4$, CH_2Cl_2, 20 °C; vi, but-3-en-2-one, tetrahydrofuran, 20 °C [48% from *E*-(**11**)]; vii, H_2, $PdCl_2$, ethanol, 20 °C (76%); viii, Jones reagent, acetone; ix, $HSCH_2CH_2SH$, BF_3·Et_2O, CH_2Cl_2, 20 °C (48%); x, W-2 Raney Ni, ethanol (61%)

the intermediacy of a nitrone has been suggested, this species could not be trapped in any other way.

We wished to extend the mild allene-based methodology described above to incorporate alkenes and alkynes and with this in mind a series of candidates for cyclization (**22a,b**) and (**23a,b**) were prepared. The olefinic oximes (**22a**)[17] and (**22b**)[18] did not react with Ag^I and were recovered unchanged for 24 h. The acetylenic substrates (**23a**) and (**23b**) were on the other hand reactive towards Ag^I but if nitrones were the initial products of these reactions their presence could not be established by the use of 1,3-dipolarophiles or hydride ion as trapping agents and no characterizable products could be isolated.



Scheme 6. *Reagents:* i, $NaBH_4$, MeOH



In summary, substituted heterocyclic nitrones may be generated in a regioselective manner by the Ag^I-promoted cyclization of γ- and δ-allenic oximes and their 1,3-dipolar cycloaddition reactions provide a stereocontrolled entry into disubstituted pyrrolidines and piperidines. The reactivity of the allenic residue appears to be crucial to the successful implementation of this approach and the scope of the process in terms of the variation of electrophile is limited to Ag^I. Nevertheless, the reactions do proceed well, given the need to use isomerically pure oxime for the best results, and the opportunity does exist to use the π-bond that is retained from the allene after cyclization, to functionalise the heterocyclic product still further.

Experimental

General.—All solvents and reagents were purified and dried by standard methods. Petroleum refers to that fraction boiling in the range 60—80 °C. M.p.s were determined with a Gallenkamp melting point apparatus and are uncorrected. Chromatographic separations were performed using Merck Kieselgel 60 (Art 9385) or Merck Kieselgel 60H (Art 7736). I.r spectra were recorded on either a Perkin-Elmer 197 or 1310 spectrometer. ^1H N.m.r. spectra were, unless otherwise stated, determined at 270 MHz on a JEOL GX270 using tetramethylsilane as internal standard in deuteriochloroform. In addition n.m.r. spectra were obtained at 60 MHz on a Perkin-Elmer R-24B and at 400 MHz on a Bruker WH400 *via* the S.E.R.C. facility at Warwick University. Mass spectra, electron impact (e.i.), and chemical ionisation (c.i.) using isobutane as the reagent gas, as well as high-resolution mass determinations (e.i. only) were recorded on a VG Analytical 707E instrument with a VG 2000 data system. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser at Bath University.

(E)- *and* (Z)-*Octa*-6,7-*dien*-2-*one Oxime* (**2a**).—A solution of acetone oxime (1.095 g, 15 mmol) in THF (15 ml) was cooled to 0 °C and a solution of butyl-lithium (1.6M in hexane; 19.5 ml, 31 mmol) was added slowly. The resulting pale yellow solution was stirred at 0 °C for 30 min after which time a solution of 5-iodopenta-1,2-diene[19] (2.8 g, 15.2 mmol) in THF (2 ml) was added slowly. After the addition was complete the reaction mixture was stirred for 45 min and then quenched with saturated aqueous NH_4Cl (10 ml) followed by water (10 ml). The mixture was extracted with ether (4 × 30 ml) and the combined extracts were dried (Na_4SO_4) and concentrated under reduced pressure. Distillation gave (**2a**) (1.5 g, 75%) as a colourless liquid, b.p. 120—124 °C (20 mmHg) and ^1H n.m.r. analysis showed that both *E*- and *Z*-(**2a**) were present in approximately equal amounts after distillation (Found: M^+, 139.098. $C_8H_{13}NO$ requires 139.099); $\nu_{max.}$(thin film) 3 300 br (OH), 1 950 and 1 640 cm^{-1}; *E*-(**2a**): δ_H 8.25 (1 H, br s, OH, exchanges with D_2O), 5.10 (1 H, quin, *J* 6.5 Hz), 4.70—4.65 (2 H, m), 2.25—2.20 (2 H, m), 2.07—1.97 (2 H, m), 1.88 (3 H, s), and 1.73—1.58 (2 H, m); *Z*-(**2a**): δ_H 8.38 (1 H, br s, OH, exchanges with D_2O), 5.13 (1 H, quin, *J* 6.5 Hz), 4.71—4.66 (2 H, m), 2.44—2.38 (2 H, m), 2.10—2.00 (2 H, m), 1.87 (3 H, s), 1.73—1.58 (2 H, m); *m/z* (e.i.) 139 (M^+), 120, and 73.

(E)- *and* (Z)-*Hepta*-5,6-*dien*-2-*one Oxime* (**2b**).—With a similar procedure to that described for the oxime (**2a**), alkylation of acetone oxime with 4-bromobuta-1,2-diene[20] gave *E*- and *Z*-(**2b**) (37%) as a colourless liquid which could be separated by chromatography (Found: M^+, 125.092. $C_7H_{11}NO$ requires 125.084); $\nu_{max.}$(thin film) 3 250 br (OH), 1 950, and 1 650 cm^{-1}; *E*-(**2b**): δ_H 8.26 (1 H, br s), 5.14 (1 H, quin, *J* 6.5 Hz), 4.74—4.68 (2 H, m), 2.54—2.44 (2 H, m), 2.30—2.17 (2 H, m), and 1.90 (3 H, s); *Z*-(**2b**): δ_H 8.38 (1 H, br s), 5.14 (1 H, quin, *J* 6.5 Hz), 4.74—4.67 (2 H, m), 2.54—2.44 (2 H, m), 2.30—2.17 (2 H, m), and 1.88 (3 H, s); *m/z* (c.i.) 126 ($M^+ + 1$).

(E)- *and* (Z)-*Hepta*-5,6-*dienal Oxime* (**3a**).—A solution of hepta-5,6-dien-1-ol[21] (1.7 g, 15 mmol) in CH_2Cl_2 (20 ml) was added with rapid stirring to an ice-cold mixture of pyridinium chlorochromate (PCC) (3.4 g, 15.8 mmol), anhydrous sodium acetate (2.3 g) and 4Å molecular sieves (1 g) in CH_2Cl_2 (50 ml). After 10 min at 0 °C additional PCC (1.7 g, 7.9 mmol) was added and the reaction mixture was allowed to warm to room temperature and then stirred for 3 h. After this time diethyl ether–hexane (1:1; 100 ml) was added and the mixture filtered through a Florisil column. The filtrate was carefully concentrated to give crude hepta-5,6-dienal as a colourless liquid was used without further purification [$\nu_{max.}$(thin film) 1960 and 1720 cm^{-1}].

This material was dissolved in methanol (20 ml) and treated with a solution of sodium acetate (6 g) and hydroxylamine hydrochloride (2 g) in water (10 ml). The mixture was heated on a steam-bath for 20 min and then allowed to stand at ambient temperature for 1 hour. Water (50 ml) was added and the product was extracted with CH_2Cl_2 (3 × 30 ml). The combined extracts were dried ($MgSO_4$) and after removal of solvent and purification of the residue by flash chromatography, the oxime (**3a**) (1.47g, 78%) was isolated as a colourless oil as a 1:1 mixture of *E*/*Z* isomers (Found: M^+, 125.088. $C_7H_{11}NO$ requires 125.084); $\nu_{max.}$(thin film) 3 320, 1 960, and 1 620 cm^{-1}; *E*-(**3a**): δ_H 8.90 (1 H, br, OH), 7.30 (1 H, t, *J* 7 Hz), 5.20 (1 H, m), 4.85—4.65 (2 H, m), and 2.50—1.45 (6 H, m); *Z*-(**3a**): δ_H 8.90 (1 H, br, OH), 6.65 (1 H, t, *J* 7 Hz), 5.20 (1 H, m), 4.85—4.65 (2 H, m), and 2.50—1.45 (6 H, m); *m/z* (e.i.) 125 (M^+).

(E)- *and* (Z)-*Hexa*-4,5-*dienal Oxime* (**3b**).—A solution of hexa-4,5-dienenitrile[10] (810 mg, 8.7 mmol) in THF (3 ml) was treated with di-isobutylaluminium hydride (DiBAl) (25% solution in toluene, 5 ml) and stirred for 20 h. After this time additional DiBAl solution (6 ml) was added and after 1 h the mixture was poured into methanol (10 ml) and a solution of hydroxylamine hydrochloride (1 g) and sodium acetate (2 g) in water (10 ml) was added. After being heated on a steam-bath for 10 min the solution was cooled to room temperature and the product was extracted with CH_2Cl_2 (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and evaporated and the residue, purified by flash chromatography to give the oxime (**3b**) (620 mg, 57%) as a colourless oil of the *E*/*Z* isomers (1:1) (Found: M^+, 111.064. C_6H_9NO requires 111.068); $\nu_{max.}$(thin film) 3 330, 1 965, and 1 620 cm^{-1}; *E*-(**3b**): δ_H 9.28 (1 H, s, OH), 7.23 (1 H, t, *J* 7 Hz), 5.15 (1 H, m), 4.75—4.50 (2 H, m), and 2.50—1.98 (4 H, m); *Z*-(**3b**): δ_H 9.28 (1 H, s, OH), 6.55 (1 H, t, *J* 7 Hz), 5.15 (1 H, m), 4.85—4.65 (2 H, m), and 2.50—1.45 (4 H, m).

6-*Methyl*-2-*vinyl*-2,3,4,5-*tetrahydropyridine* 1-*Oxide* (**4**).—To a solution of the oxime *E*-(**2a**) (80 mg, 0.57 mmol) in CH_2Cl_2 (2 ml) was added $AgBF_4$ (111 mg, 0.57 mmol). The solution was stirred at room temperature for 30 min after which 2M NaOH (2 ml) was added and the mixture extracted with ethyl acetate (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure and the residue purified by chromatography to give, on elution with chloroform–hexane (5:1), the nitrone (**4**) (40 mg, 50%) as a colourless oil (Found: M^+, 139.098. $C_8H_{13}NO$ requires 139.099); $\nu_{max.}$(thin film) 1 630 and 1 610 cm^{-1}; δ_H 5.98 (1 H, ddd, *J* 16, 10, 6 Hz), 5.30 (1 H, br d, *J* 10 Hz), 5.28 (1 H, br d, *J* 16 Hz), 4.40 (1 H, m), 2.48—2.43 (2 H, m), 2.11 (3 H, s), 2.08—1.80 (2 H, m), and 1.86—1.63 (2 H, m); *m*/*z* (e.i.) 139 (M^+).

5-*Methyl*-2-*vinyl*-3,4-*dihydro*-2H-*pyrrole* 1-*Oxide* (**5**).—With a similar procedure to that described above, cyclisation of (**2b**) gave the nitrone (**5**) as a colourless oil (74%) (Found: M^+, 125.084. $C_7H_{11}NO$ requires M^+, 125.084); $\nu_{max.}$(thin film), 1 700 and 1 620 cm^{-1}; δ_H ($CDCl_3$) 6.00 (1 H, m), 5.50 (1 H, br d, *J* 14 Hz), 5.44 (1 H, br d, *J* 7 Hz), 4.88 (1 H, m), 3.20—2.79 (2 H, m), 2.59 (1 H, m), 2.24 (3 H, s), and 1.99 (1 H, m); *m*/*z* (e.i.) 125(M^+).

5-*Methyl*-2-*vinyl*-5,6-*dihydro*-4H-1,2-*oxazine* (**6**).—To a solution of *Z*-(**2b**) (150 mg, 1.2 mmol) in CH_2Cl_2 (5 ml) was added $AgBF_4$ (230 mg, 1.2 mmol). The solution was stirred in the dark for 16 h and then diluted with ethyl acetate (10 ml) and washed with 2M NaOH (5 ml). The organic solution was dried ($NaSO_4$) and concentrated under reduced pressure and the residue purified by chromatography to give, on elution with hexane–ether (2:1), the dihydro-oxazine (**6**) (50 mg, 34%) as a colourless oil (Found: M^+, 125.085. $C_7H_{11}NO$ requires 125.084); $\nu_{max.}$(thin film) 1 630 and 1 620 cm^{-1}; δ_H 5.88 (1 H, ddd, *J* 5, 10, 17 Hz), 5.35 (1 H, br d, *J* 17 Hz), 5.25 (1 H, br d, *J* 10 Hz), 4.16 (1 H, m), 2.30—2.09 (2 H, m), 1.91 (3 H, s), and 2.03—1.70 (2 H, m); δ_C ($CDCl_3$) 155.0 (CN), 136.2 (*C*H=CH$_2$), 117.1 (CH=*C*H$_2$), 74.3 (0CH), 24.1 and 24.0 (ring-CH_2), and 21.6 (CH_3); *m*/*e* (e.i) 125 (M^+), 95, and 66.

General Procedure for the Generation and 1,3-Dipolar Cycloaddition of 2-*Vinyl*-2,3,4,5-*tetrahydropyridine* 1-*Oxide* (**7**).—Silver tetrafluoroborate (67 mg, 0.34 mmol) was added to a solution of the oxime (**3a**) (63 mg, 0.5 mmol (1:1 mixture of *E*/*Z* isomers) in CH_2Cl_2 (3 ml). After 2 h the dipolarophile (2—5 equiv.) was added and the reaction mixture was stirred for 48—72 h at room temperature. Ethyl acetate (10 ml) was then added and the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (5 ml). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and the product was purified by flash chromatography. All cycloadducts (**8a**—**e**) were isolated as colourless oils and the yields obtained are shown in Table 1.

(2α,3aβ,7α)-2-*Phenyl*-7-*vinylhexahydro*-2H-*isoxazolo*[2,3-a]-*pyridine* (**8a**). (Found: M^+, 229.146. $C_{15}H_{19}NO$ requires 229.146); $\nu_{max.}$(thin film) 1 620 and 1 600 cm^{-1}; δ_H (400 MHz) 7.40—7.23 (5 H, m), 5.89 (1 H, m, C*H*=CH$_2$), 5.33 (1 H, dd, *J* 10, 4 Hz, H$_2$), 5.22 (1 H, dd, *J* 15, 4 Hz, *E*-CH=C*H*$_2$), 5.11 (1 H, dd, *J* 10, 4 Hz, CH=C*H*$_2$), 3.90 (1 H, m, 3a-H), 3.23 (1 H, m, 7-H), 2.74 (1 H, td, *J* 12, 10 Hz, 3α-H), 2.07 (1 H, m), 1.98 (1 H, m), 1.90 (1 H, m), 1.70 (1 H, m), 1.56 (1 H, m), and 1.52—1.41 (2 H, m); *m*/*z* (e.i.) 229 (M^+).

Ethyl(2α,3aβ,7α)-7-*Vinylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine*-2-*carboxylate* (**8b**). (Found: M^+, 225.135. $C_{12}H_{19}NO_3$ requires *M*, 225.136); $\nu_{max.}$(thin film) 1 740 and 1 645 cm^{-1}; δ_H (400 MHz) 5.85 (1 H, m, CH=CH$_2$), 5.16 (1 H, dd, *J* 17, 2 Hz, *E*-CH=C*H*$_2$), 5.09 (1 H, dd, *J* 10, 2 Hz, *Z*- CH=C*H*$_2$), 4.73 (1 H, dd, *J* 9, 4 Hz, H$_2$), 4.16 (2 H, d, *J* 7 Hz, $CO_2CH_2CH_3$) 3.70 (1 H, m, 3aα-H), 3.01 (1 H, m, 7α-H), 2.59 (1 H, dt, *J* 10, 13 Hz, 3aα-H), 2.21 (1 H, ddd, *J* 13, 7, 3 Hz, 3β-H), 2.02 (1 H, m, 4α-H or 4β-H), 1.90 (1 H, m, 4α-H or 4β-H), 1.65-1.37 (4H, 6α/β-H 8α/β-H), and 1.25 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$); *m*/*z* (e.i.) 225 (M^+), 198, and 152. N.O.e difference spectra were carried out at −50 °C. Irradiation at (a) δ 3.01 (7α-H) resulted in an enhancement of 2α-H, 3α-H and -C*H*=CH$_2$; (b) δ 3.70 (3aβ-H) resulted in an enhancement of 3β-H and 4β-H; (c) δ 4.73 (2α-H) resulted in an enhancement of 7α-H and 3α-H.

(3aα,6α,9aβ,9bα)-6-*Vinyldecahydrocyclopent*[4,5]*isoxazolo*-[2,3-a]*pyridine* (**8c**). (Found: M^+, 193.145. $C_{12}H_{19}NO$ requires *M*, 193.146); $\nu_{max.}$(thin film) 1620 cm^{-1}; δ_H (400 MHz) 5.84 (1 H, m, C*H*=CH$_2$), 5.15 (1 H, br d, *J* 15 Hz, *E*-CH=C*H*$_2$), 5.07 (1 H, br d, *J* 10 Hz, *Z*-CH=C*H*$_2$), 4.78 (1 H, t, *J* 7 Hz,3aα-H), 3.15 (1 H, m, 6α-H), 3.07 (1 H, dd, *J* 8, 5 Hz, 9aα-H), 2.83 (1 H, br q, *J* 8 Hz, 9bα-H), 2.02—1.80 (4 H, m), and 1.75—1.30 (8 H, m); *m*/*z* (e.i.) 193 (M^+), 166, and 126.

(3aα,6α,9aβ,9bα)-6-*Vinyl*-1,3a,6,7,8,9a,9b-*octahydrocyclopent*[4,5]*isoxazolo*[2,3-a]*pyridine* (**8d**). (Found: M^+, 191.296. $C_{12}H_{17}NO$ requires *M*, 191.130); $\nu_{max.}$(thin film) 1640 cm^{-1}; δ_H (400 MHz) 5.86 (1 H, m, C*H*=CH$_2$), 5.80—5.76 (2 H, 2-H and 3-H, CH=CH), 5.38 (1 H, br d, *J* 10 Hz, 3aα-H), 5.17 (1 H, br d, *J* 15 Hz, *E*-CH=C*H*$_2$), 5.08 (1 H, br d, *J* 10 Hz, *Z*-CH=C*H*$_2$), 3.15 (1 H, m, 6α-H), 3.06 (1 H, tq, *J* 8, 1.5 Hz, 9bα-H), 2.98 (1 H, ddd, *J* 10, 5, 2 Hz, 9aβ-H), 2.51 (1 H, dd, *J* 15, 8 Hz, 1α-H or 1β-H) 2.13 (1 H, br, d, *J* 15 Hz, 1α-H or 1β-H), 1.99 (1 H, m), 1.86 (1 H, m), 1.78 (1 H, m), and 1.60—1.36 (3 H, m); *m*/*z* (e.i.) 191 (M^+, 10%) and 126 (100%). N.O.e experiments involved irradiations at (a) δ 3.06 (9bα-H) resulted in an enhancement of 3aα-H and 1α-H); (b) δ 3.15 6α-H resulted in an enhancement of 3aα-H; δ 5.38 (3aα-H) resulted in an enhancement of 6α-H.

Treatment of (**8d**) with iodomethane in ether gave the corresponding methiodide salt which was recrystallised from methanol–ethyl acetate to give crystals suitable for *X*-ray crystallographic analysis.

(4aα,7α,10aβ,10bα)-7-*Vinyl*-2,4a,7,8,9,10,10a,10b-*octahydro*-1H-*pyrido*[1,2-b][1,2]*benzisoxazole* (**8e**). (Found: M^+, 205.147, $C_{13}H_{19}NO$ requires *M*, 205.146); $\nu_{max.}$(thin film) 1 622 cm^{-1}; δ_H (400 MHz) 5.96 (1 H, m); 5.84 (1 H, m, C*H*=CH$_2$), 5.75 (1 H, m), 5.19 (1 H, br d, *J* 15 Hz, *E*-CH=C*H*$_2$), 5.10 (1 H, br d *J* 10 Hz, *Z*-CH=C*H*$_2$), 4.73 (1 H, br d, *J* 6 Hz, 4a-H), 3.37 (1 H, dd, *J* 10, 5, Hz, 10a-H), 3.18 (1 H, m, 7-H), 2.69 (1 H, m, 10b-H), 2.06—1.80 (5 H, m), 1.65 (1 H, m) and 1.55—1.37 (4 H, m); *m*/*z* (e.i.) 195 (M^+).

Treatment of (**8e**) with iodomethane in ether gave the corresponding methiodide salt which was recrystallised from methanol–ethyl acetate to give crystals suitable for *X*-ray crystallographic analysis.

General Procedure for Generation and Cycloaddition of 2-

Vinyl-3,4-dihydro-2H-pyrrole 1-Oxide (**9**).—A solution of (**2b**) (110 mg, 1 mmol), (1:1 mixture of *E*/*Z* isomers) in 1,2-dichloroethane (5 ml) was treated with silver tetrafluoroborate (196 mg, 1 mmol). After 5 min the 1,3-dipolarophile (styrene, methyl vinyl ketone) (2—4 equiv.) was added and the solution was heated at 70 °C for 2 h to effect cycloaddition. Following the work-up procedure described for the cycloadducts (**8a—e**), the products (**10a,b**) were isolated by flash chromatography. An additional product was observed during the initial cyclisation of the oxime (**3b**). This was presumed to be the corresponding dihydroxazine (**11**), but this material could not be isolated in pure form.

The nitrone (**9**) was also isolated following the reaction of (**3b**) with $AgBF_4$ in 1,2-dichloroethane for 5 min. After purification by flash chromotography, during which a considerable amount of material was lost, the nitrone (**9**) was isolated as a colourless oil ($\nu_{max.}$(thin film) 1 620 and 1 590 cm^{-1}; δ_H (60 MHz), 6.75 (1 H, br s), 5.80 (1 H, m), 5.10—5.29 (2 H, m), 4.36 (1 H, m), and 2.82—1.80 (4 H, m)].

(2α,3aβ,6α)-2-*Phenyl*-6-*Vinylhexahydropyrrolo*[1,2-b]*isoxazole* (**10a**). Isolated in 42% yield (Found: M^+, 215.131. $C_{14}H_{17}NO$ requires 215.131); $\nu_{max.}$(thin film) 1 620, and 1 600 cm^{-1}; δ_H (400 MHz) 7.46—7.17 (5 H, m), 5.85 (1 H, m, C*H*=CH_2), 5.19 (1 H, br d, *J* 15 Hz, *E*-C*H*$_2$), 5.05 (1 H, br d, *J* 10 Hz, *Z*-CH=C*H*$_2$), 4.97 (1 H, dd, *J* 10, 6 Hz, 2α-H), 3.91 (1 H, qd, *J* 7, 3 Hz, 3aβ-H), 3.58 (1 H, m, 6α-H), 2.30-2.19 (2 H, m, 1α-H and 1β-H), 2.09 (1 H, m, 4β-H) 1.94 (1 H, m, 5α-H) and 1.65—1.50 (2 H, m, 4α-H and 5β-H); *m*/*z* (e.i.) 215 (M^+), 111, and 104. Irradiation of (i) δ 3.58 (6α-H) resulted in enhancement of 2α-H and 5α-H and (ii) δ 3.91 (3aβ-H) resulted in enhancement of 1βH and 4β-H.

(2α,3aβ,6α)-6-*Vinylhexahydropyrrole*[1,2-b]*isoxazol*-2-*ylethanone* (**10b**). Isolated in 36% yield (Found: M^+, 181.112. $C_{10}H_{15}NO_2$ requires 181.110); $\nu_{max.}$(thin film) 1 720 and 1 620 cm^{-1}; δ_H(400 MHz) 5.83 (1 H, m), 5.24 (1 H, br d, *J* 15 Hz), 5.13 (1 H, br d, *J* 10 Hz), 4.46 (1 H, dd, *J* 8, 7 Hz 2α-H), 3.74 (1 H, m), 3.64 (1 H, m), 2.50 (1 H, dt, *J* 12, 7 Hz), 2.26 (3 H, s), 2.17 (1 H, m), 2.11—2.03 (2 H, m), and 1.70—1.55 (2 H, m); *m*/*z* (e.i.) 181 (M^+).

Synthesis of (E)- *and* (Z)-*Undeca-4,5-dienal Oxime* (**12**).—*Ethyl deca-3,4-dienoate*. By the general procedure described by Crandall and Tindell,[22] oct-1-yn-3-ol (3.5 g, 27.7 mmol) was dissolved in triethyl orthoacetate (10 ml) containing pivalic acid (150 mg) and the mixture was heated under an atmosphere of nitrogen at 115—120 °C for 48 h. The excess of solvent was removed under reduced pressure and ethyl acetate (50 ml) was added. The solution was then washed with saturated aqueous sodium hydrogen carbonate (10 ml), dried (Na_2SO_4), and evaporated and then distilled to give ethyl deca-3,4-dienoate (4.3 g, 79%), b.p. 100 °C/0.05 mmHg (bulb-to-bulb) (Found: M^+, 196.146. $C_{12}H_{20}O_2$ requires 196.146); $\nu_{max.}$(thin film) 1 945 and 1 768 cm^{-1}; δ_H(60 MHz), ($CDCl_3$) 5.30—4.90 (2 H, m), 4.05 (2 H, q, *J* Hz), 3.04—2.78 (4 H, m), and 1.68—0.90 (12 H, m).

Deca-3,4-dienol. To a suspension of lithium aluminium hydride (200 mg, 5 mmol) in dry ether (50 ml) at −60 °C was added a solution of ethyl deca-3,4-dienoate (1.0 g, 5.1 mmol) in ether (15 ml). The mixture was allowed to warm to room temperature and after being stirred for 10 min was recooled to −10 °C. Water (0.9 ml) and 2M aqueous sodium hydroxide (0.2 ml) were then added. The resulting slurry was filtered through elite, and the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to give deca-3,4-dienol (763 mg, 97%) as a colourless liquid which was used without further purification; $\nu_{max.}$(thin film) 3 320 and 1 960 cm^{-1}; δ_H (60 MHz), CCl_4) 5.29—4.88 (2 H, m), 3.59 (2 H, t, *J* 7 Hz), 3.00 (1 H, s, OH, exchanges with D_2O), 2.45—1.80 (4 H, m), and 1.70—0.66 (9 H, m).

Undeca-4,5-dienenitrile. Deca-3,4-dienol (700 mg, 4.5 mmol) was dissolved in dry pyridine (4 ml), cooled to 0 °C, and toluene-*p*-sulphonyl chloride (1.29 g, 6.7 mmol) and 4-dimethylaminopyridine (10 mg) were added. After 10 min the reaction mixture was diluted with ether (50 ml), and this solution was then washed with 2M hydrochloric acid (3 × 10 ml), and saturated aqueous sodium hydrogen carbonate (10 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The crude tosylate was then dissolved in dimethyl sulphoxide (25 ml) and sodium cyanide (1.0 g, 20 mmol) was added. After the mixture had been stirred at 75 °C for 2.5 h, water (50 ml) was added and the product was extracted with ether (3 × 50 ml). The combined extracts were washed with water (3 × 10 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Following filtration of the residue through a column of silica gel, undecadiene-4,5-nitrile (580 mg, 78%) was isolated as a colourless liquid. The vile odour associated with this material prevented characterisation by elemental analysis; $\nu_{max.}$(thin film) 2250 and 1960 cm^{-1}; δ_H (60 MHz, CCl_4) 5.40—4.95 (2 H, m), 2.50—1.80 (4 H, m), and 1.65—0.60 (11 H, m).

(E)- *and* (Z)-*Undeca-4,5-dienal oxime* (**12**). Di-isobutylaluminium hydride (DiBAI) (25% solution in toluene; 1.2 ml, 2.12 mmol) was added to a stirred solution of undeca-4,5-dienenitrile (290 mg, 1.77 mmol) in ether (10 ml). After 1 h, water (0.5 ml) was added and after a further 10 min a solution of hydroxylamine hydrochloride (200 mg) and sodium acetate (500 mg) in water (2 ml) was added. After the mixture had been rapidly stirred for 20 min the product was extracted with ether (3 × 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated and the product was purified by flash chromatography to give (**12**) (243 mg, 76%) as a 1:1 mixture of *E*- and *Z*-isomers (Found: C, 73.0; H, 10.85; N, 7.9. $C_{11}H_{19}NO$ requires C, 72.88; H, 10.56; N, 7.73%); $\nu_{max.}$(thin film) 3 200br, 1 960, and 1 620 cm^{-1}; δ_H(both isomers) 9.2 (1 H, br s, OH, exchanges with D_2O), 7.44 (1/2H, t, *J* 6 Hz, *E*-CH=N), 6.74 (1/2 H, t, *J* 6 Hz, *Z*-CH=N), 5.20—5.02 (2 H, m), 2.55—2.24 (2 H, m), 2.20—2.15 (2 H, m), 2.06—1.90 (2 H, m), 1.46—1.10 (6 H, m) and 0.87 (3 H, t, *J* 7 Hz); *m*/*z* (e.i.) 181 (M^+, 2%), 164 (20%), and 67 (100%) (Found: M^+, 181.142. $C_{11}H_{19}NO$ requires 181.146). Some separation of *E*-(**12**) and *Z*-(**12**) was achieved by chromatography, the less polar *E*-isomer being eluted with hexane–ether (8:1); the *Z*-isomer was then eluted. The latter when dissolved in chloroform equilibrated back to a 1:1 mixture of isomers overnight.

6-(*Hept-1-enyl*)-5,6-*dihydro*-4H-1,2-*oxazine* (**19**) *and* 2-(*Hept-2-enyl*)-3,4-*dihydro*-2H-*pyrrole-Oxide* (**13**).—Silver tetrafluoroborate (78 mg, 0.4 mmol) was added to a solution of (**12**) (70 mg, 0.39 mmol), (6:4 mixture of *E*/*Z* isomers) in CH_2Cl_2 (5 ml). After 1 h, ethyl acetate (20 ml) and water (5 ml) were added. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography gave, on elution with ether–hexane (1 : 1), the dihydro-oxazine (**19**) [25 mg, 89% based on *Z*-(**12**)] (Found: M^+, 181.141. $C_{11}H_{19}NO$ requires 181.146); $\nu_{max.}$(thin film) 1 660 and 1 618 cm^{-1}; δ_H 7.22 (1 H, br s), 5.83 (1 H, dtd, *J* 15, 7, 1 Hz), 5.49 (1 H, ddt, *J* 15, 7, 1.5 Hz), 4.21 (1 H, m), 2.38—1.90 (4 H, m), 1.85—1.70 (2 H, m), 1.45—1.20 (6 H, m), and 0.89 (3 H, t, *J* 7 Hz); *m*/*z* (e.i.) 181 (M^+), 67. Continued elution using $CHCl_3$–MeOH (5:1) gave the nitrone (**13**) [36 mg, 86% based on *E*-(**12**)] (Found: M^+, 181.142, $C_{11}H_{19}NO$ requires 181.146); $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1}; δ_H 6.86 (1 H, br s), 5.85 (1 H, m), 5.56 (1 H, m), 4.45 (1 H, m), 2.72—2.61 (2 H, m), 2.54—2.40 (1 H, m), 2.22—1.92 (3 H, m), 1.50—1.10 (6 H, m), and 0.88 (3 H, t *J* 7 Hz); *m*/*z* (e.i.) 181 (M^+), 164 and 67.

(E)-(2α,3aβ,6α)-1-{6-(*Hept-1-enyl*)*hexahydropyrrolo*[1,2-b]-

Table 2. Crystal data, details of intensity measurements and structure refinement for (**8d**)·MeI (**8e**)·MeI

Complex	(**8d**)·MeI	(**8e**)·MeI
Formula	$C_{13}H_{20}INO$	$C_{14}H_{22}INO$
M	333.21	347.24
Crystal system	Monolinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a/Å	9.123(1)	12.473(1)
b/Å	12.626(1)	15.614(1)
c/Å	12.073(1)	7.699(1)
β/°	95.10(1)	96.73(1)
U/Å^3	1 385.2(2)	1 489.1(3)
Z	4	4
D_c/g cm^{-3}	1.598	1.549
F(000)	664	696
Crystal size/mm	0.63 × 0.35 × 0.30	0.38 × 0.38 × 0.13
μ/cm^{-1}	22.7	21.1
Absorption corr. (min., max.)	87%, 100%	70%, 100%
2θ-range/°	3.0, 56.0	3.0, 50.0
h, k, l range	0 ⟶ 12, 0 ⟶ 16, −15 ⟶ 15	0 ⟶ 14, 0 ⟶ 18, −9 ⟶ 9
Intensity variation	<3%	<3%
Total no. of reflections	3690	2839
No. of unique reflections	3330	2598
Significance test	$F_0 > 6.0\sigma(F_0)$	$F_0 > 6.0\sigma(F^0)$
No. of reflections used in the refinement	2817	1956
No. of refined parameters	225	242
Max. least-squares shift-to-error ratio	0.001	0.001
Min. and Max. height in final difference Fourier map, e/e Å^{-3}	−0.57, 0.54	−0.09, 0.14
Function minimized	$\Sigma_w(\|F_0\| - \|F_c\|)^2$	$\Sigma_w(\|F_0\| - \|F_c\|F_c\|)^2$
Weighting scheme parameter g in $w = 1/[\delta^2(F_0) + gF_0^2]$	0.0001	0.0001
Final R	0.021	0.019
Final R_w	0.024	0.021

Table 3. Fractional atomic co-ordinates (× 10^4) for (**8d**)·MeI

	x	y	z
I	275.3(2)	2 208.2(1)	2 937.6(1)
O	−246(2)	−3 500(1)	838(1)
N	−99(2)	−4 019(1)	1 896(1)
C(1)	−1 618(2)	−4 455(2)	2 132(2)
C(2)	−1 591(3)	−4 785(2)	3 347(2)
C(3)	−1 145(3)	−3 870(2)	4 129(2)
C(4)	362(3)	−3 451(2)	3 905(2)
C(5)	448(2)	−3 140(2)	2 694(2)
C(6)	−446(2)	−2 185(2)	2 268(2)
C(7)	495(3)	−1 163(2)	2 318(2)
C(8)	751(3)	−966(2)	1 138(3)
C(9)	61(3)	−1 628(2)	439(2)
C(10)	−804(3)	−2 424(2)	1 024(2)
C(11)	−2 065(3)	−5 332(2)	1 333(2)
C(12)	−3 108(3)	−5 224(3)	532(2)
C(13)	1 030(3)	−4 860(2)	1 797(2)

isoxazol-2-yl}ethanone (**14a**) *and* (E)-(2β,3aβ,6α)-1-{6-(*hept-1-enyl*)*hexahydropyrrolo*[1,2-b]*isoxazol-2-yl}ethanone* (**14b**).—Silver tetrafluoroborate (250 mg, 1.28 mmol) was added to a solution of the oxime (**12**) (260 mg, 1.44 mmol), (85:15 ratio of E/Z isomers) in CH_2Cl_2 (30 ml). The mixture was stirred at room temperature and then worked up as described above to give the nitrone (**13**) [175 mg, 79% based on *E*-(**12**)]. This was dissolved in THF (10 ml) and methyl vinyl ketone (300 mg, 2.86 mmol) was added. The mixture was stirred for 15 h, and then evaporated and purified by flash chromatography to give, on elution with ether–hexane (1:4), the cycloadduct (**14a**) (54 mg, 22%) as a colourless oil (Found: M^+, 251.188. $C_{15}H_{25}NO_2$ requires 251.188); $\nu_{max.}$(thin film) 1 760 cm^{-1}; δ_H (400 MHz) 5.64 (1 H, dtd, J 15, 6.5, 1 Hz, CH=C*H*CH$_2$), 5.43 (1 H, ddt, J 15, 8, 1 Hz, C*H*=CHCH$_2$), 4.43 (1 H, t, J 7 Hz, 2α-H), 3.74 (1 H, m 3aβ-H), 3.60 (1 H, m, 6α-H), 2.46 (1 H, ddd, J 13, 8, 7 Hz, 3β-H), 2.26 (3 H, s, $COCH_3$), 2.17 (1 H, ddd, J 13, 8, 5 Hz, 3α-H), 2.10—1.97 (4 H, m), 1.60 (2 H, m), 1.39—1.23 (6 H, m), and 0.86 (3 H, t, J 7 Hz); m/z (e.i.) 251 (M^+).

Continued elution gave the cycloadduct (**14b**) (64 mg, 26%) as a colourless oil (Found: M^+, 251.187. $C_{15}H_{25}NO_2$ requires 251.188); $\nu_{max.}$(thin film) 1 760 cm^{-1}; δ_H (400 MHz) 5.60 (1 H, dtd, J 15, 8, 1, CH=CHCH$_2$), 5.38 (1 H, ddt, J 15, 7, 1.5 Hz, CH=CHCH$_2$) 4.45 (1 H, t, J 8Hz, 2β-H), 3.80 (1 H, m 3aβ-H), 3.56 (1 H, m, 6α-H), 2.59 (1 H, dt, J 13, 8 Hz, 3β-H), 2.27 (3 H, s, $COCH_3$), 2.16—1.97 (5 H, m), 1.70—1.61 (2 H, m), 1.38—1.20 (6 H, m), and 0.85 (3 H, t, J 7 Hz); m/z (e.i.) 251 (M^+).

(3′β,5′β,7′aβ)-5′-*Heptyl*-3′-*methylspiro*[1,3-*dithiolane*-2,2′-*hexahydropyrrolizine*].—A solution of (**14a**) (60 mg, 0.263 mmol) in ethanol (2 ml) containing $PdCl_2$ (5 mg) was stirred under hydrogen (1 atm) for 4 h. Ether (10 ml) was added and the mixture was washed with 2M sodium hydroxide (1 ml), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography gave the alcohol (**15a**) (41 mg, 76%) as a colourless oil which was used without further purification [$\nu_{max.}$(thin film) 3350 cm^{-1}; m/z (e.i.) 239 (M^+)]. The alcohol thus prepared was dissolved in acetone (2 ml) and treated with a slight excess of Jones reagent. After completion of the reaction, filtration of the reaction mixture through a short silica column gave the amino ketone (**16**) [$\nu_{max.}$(thin film) 1760 cm^{-1}] which was immediately dissolved in CH_2Cl_2 (5 ml) containing ethane-1,2-dithiol (100 mg, 1.06 mmol) and BF_3·Et_2O (100 mg). After 2.5 h, ether (15 ml) was added and the solution was washed with 1M sodium hydroxide (2 × 1 ml), dried (Na_2SO_4), and evaporated. Purification of the residue by flash chromatography gave the dithiolane (**17**) (31 mg, 42% from cycloadduct (**14a**) (Found: M^+, 313.191. $C_{17}H_{31}NS_2$ requires 313.190); δ_H (400 MHz) 3.62 (1 H,

Table 4. Bond lengths and angles for (**8d**)·MeI

Bond lengths (Å)			
N–O	1.432(3)	C(10)–O	1.475(4)
C(1)–N	1.541(4)	C(5)–N	1.524(5)
C(13)–N	1.491(4)	C(2)–C(1)	1.522(5)
C(11)–C(1)	1.502(5)	C(3)–C(2)	1.525(5)
C(4)–C(3)	1.519(5)	C(5)–C(4)	1.522(5)
C(6)–C(5)	1.519(5)	C(7)–C(6)	1.548(5)
C(10)–C(6)	1.538(5)	C(8)–C(7)	1.486(5)
C(9)–C(8)	1.308(5)	C(10)–C(9)	1.494(4)
C(12)–C(11)	1.302(5)		

Bond angles (°)			
C(10)–O–N	107.0(2)	C(1)–N–O	108.3(2)
C(5)–N–O	103.3(2)	C(5)–N–C(1)	113.1(2)
C(13)–N–O	105.3(3)	C(13)–N–C(1)	113.6(3)
C(13)–N–C(5)	112.3(3)	C(2)–C(1)–N	109.7(3)
C(11)–C(1)–N	110.0(3)	C(11)–C(1)–C(2)	113.4(3)
C(3)–C(2)–C(1)	111.7(3)	C(4)–C(3)–C(2)	110.5(3)
C(5)–C(4)–C(3)	112.7(3)	C(4)–C(5)–N	112.1(3)
C(6)–C(5)–N	103.2(2)	C(6)–C(5)–C(4)	117.2(3)
C(7)–C(6)–C(5)	111.7(3)	C(10)–C(6)–C(5)	103.7(3)
C(10)–C(6)–C(7)	105.7(3)	C(8)–C(7)–C(6)	103.7(3)
C(9)–C(8)–C(7)	113.8(3)	C(10)–C(9)–C(8)	111.6(3)
C(6)–C(10)–O	106.4(3)	C(9)–C(10)–O	110.1(3)
C(9)–C(10)–C(6)	104.8(3)	C(12)–C(11)–C(1)	122.6(3)

Table 5. Fractional atomic co-ordinates ($\times 10^4$) for (**8e**)·MeI

	x	*y*	*z*
I	2 475.9(2)	1 454.3(1)	532.1(2)
O	3 554(2)	4 421(1)	9 367(3)
N	3 865(2)	4 056(1)	7 798(3)
C(1)	4 346(2)	3 162(2)	8 234(4)
C(2)	4 477(3)	2 685(2)	6 555(5)
C(3)	3 412(3)	2 605(3)	5 401(5)
C(4)	2 935(3)	3 487(3)	4 971(4)
C(5)	2 815(2)	4 026(2)	6 580(4)
C(6)	2 006(2)	3 739(2)	7 796(4)
C(7)	839(3)	4 007(2)	7 178(5)
C(8)	642(3)	4 951(3)	7 366(6)
C(9)	1 084(3)	5 264(2)	9 130(6)
C(10)	1 877(3)	4 889(2)	10 125(5)
C(11)	2 450(2)	4 117(2)	9 567(4)
C(12)	5 356(3)	3 244(2)	9 470(5)
C(13)	5 378(4)	3 134(3)	11 135(6)
C(14)	4 666(3)	4 663(2)	7 215(5)

m, 7aβ-H), 3.28—3.18 (4 H, m, 3-H and 4-H), 2.98 (1 H, q, *J* 6 Hz, 3′α-H), 2.70 (1 H, m, 5′α-H), 2.50 (1 H, dd, *J* 12, 6 Hz, 1′β-H), 1.99 (1 H, dd, *J* 12, 9 Hz, 1α-H), 2.03—1.90 (2 H, m), 1.54—1.41 (3 H, m) 1.30—1.19 (11 H, m), 1.21 (3 H, d, *J* 6 Hz, $CHCH_3$) and 0.86 (3 H, t, *J* 7 Hz); *m/z* (e.i.) 31 (M^+), 252, and 84. Reactions of the cycloadduct (**14b**) gave the dithiolane (**17**) in 43% overall yield. Spectral data obtained for (**17**) produced from (**14b**) was identical with that producted from the epimeric cycloadduct (**14a**).

(3α,5α,7aβ)-3-*Heptyl*-5-*methylpyrrolizine* (**18**).—A solution of the dithiolane (**17**) (10 mg, 0.032 mmol) in ethanol (0.5 ml) was treated with an excess of Raney Ni as a suspension in ethanol. After the mixture had been stirred for 2.5 h t.l.c. analysis showed that reaction was complete and ether (10 ml) was added. The mixture was washed with 2M sodium hydroxide (1 ml) and dried (K_2CO_3). The solution was filtered and the filtrate was treated with an excess of ethereal HCl. Removal of the solvent and purification of the residue by chromatography (MeOH–$CHCl_3$ 5:95) gave (**18**) as the corresponding hydrochloride salt. Neutralisation of this salt with 1M aqueous sodium hydroxide and extractions with ethyl acetate gave (**18**) (4 mg, 56%) as a colourless oil. Spectral data (i.r., m.s., ^1H and ^{13}C n.m.r.) of (**18**) were identical with those previously reported; an authentic sample of (**18**), which was used for comparative purposes, was prepared using the procedure described by Jones *et. al.*[13]

Table 6. Bond lengths and angles for (**8e**)·MeI

Bond lengths (Å)			
N–O	1.430(4)	C(11)–O	1.481(4)
C(1)–N	1.541(6)	C(5)–N	1.520(5)
C(14)–N	1.484(5)	C(2)–C(1)	1.517(6)
C(12)–C(1)	1.493(5)	C(3)–C(2)	1.514(7)
C(4)–C(3)	1.522(7)	C(5)–C(4)	1.519(6)
C(6)–C(5)	1.522(6)	C(7)–C(6)	1.536(6)
C(11)–C(6)	1.529(6)	C(8)–C(7)	1.505(7)
C(9)–C(8)	1.487(7)	C(10)–C(9)	1.316(6)
C(11)–C(10)	1.490(6)	C(13)–C(12)	1.291(7)

Bond angles (°)			
C(11)–O–N	107.9(3)	C(1)–N–O	108.3(3)
C(5)–N–O	103.6(3)	C(5)–N–C(1)	113.0(3)
C(14)–N–O	105.1(3)	C(14)–N–C(1)	112.7(3)
C(14)–N–C(5)	113.3(3)	C(2)–C(1)–N	109.7(3)
C(12)–C(1)–N	109.8(3)	C(12)–C(1)–C(2)	114.7(4)
C(3)–C(2)–C(1)	111.5(4)	C(4)–C(3)–C(2)	110.3(4)
C(5)–C(4)–C(3)	113.4(4)	C(4)–C(5)–N	111.1(3)
C(6)–C(5)–N	102.4(3)	C(6)–C(5)–C(4)	118.4(4)
C(7)–C(6)–C(5)	113.7(4)	C(11)–C(6)–C(5)	103.8(3)
C(11)–C(6)–C(7)	113.7(4)	C(8)–C(7)–C(6)	113.3(4)
C(9)–C(8)–C(7)	111.3(4)	C(10)–C(9)–C(8)	123.9(4)
C(11)–C(10)–C(9)	123.0(4)	C(6)–C(11)–O	106.0(3)
C(10)–C(11)–O	104.7(3)	C(10)–C(11)–C(6)	115.7(4)
C(13)–C(12)–C(1)	122.7(5)		

(E)- *and* (Z)-*Hex*-5-*yn*-2-*one Oxime* (**23a**).—With a similar procedure to that described for the oxime (**2a**), alkylation[9] of acetone oxime with 3-bromopropyne gave (**23a**) in 67% yield, b.p. 80 °C (0.04 mmHg, bulb-to-bulb), m.p. 43—43.5 °C (Found: C, 64.8; H, 8.37; N, 12.8. C_6H_9NO requires C, 64.86; H, 8.11; N, 12.60%); $\nu_{max.}$(thin film) 3 250 br. (OH), 2 120, and 1 650 cm^{-1}; *E*-(**23a**): δ_H 8.50 (1 H, br. s, OH) 2.44—2.42 (4 H, m), 1.99 (1 H, m), and 1.92 (3 H, s); *Z*-(**23a**): δ_H 7.00 (1 H, br. s, OH), 2.64—2.57 (2 H, m), 2.49—2.42 (2 H, m), 1.99 (1 H, t, *J* 2.5 Hz), and 1.95 (3 H, s); *m/z* (c.i.) 112 ($M^+ + 1$).

(E)- *and* (Z)-*Pent*-4-*ynol Oxime* (**23b**).—With a similar procedure, alkylation[23] of acetaldehyde oxime with 3-bromopropyne gave (**23b**) in 23% yield, m.p. 46—47 °C, b.p. 90 °C (1 mm Hg, bulb-to-bulb) (Found: C, 61.4; H, 7.3; N, 14.0. C_5H_7NO requires C, 61.8; H, 7.2; N, 14.4%); $\nu_{max.}$(thin film) 3 025 br (OH), 2 105, and 1 650 cm^{-1}; *E*-(**23b**): δ_H 8.90 (1 H, br s, OH, exchanges with D_2O), 7.51 (1 H, t, *J* 4.5 Hz), 2.68—2.58 (2 H, m), 2.45—2.35 (2 H, m), and 2.01 (1 H, t, *J* 2.5 Hz); *Z*-(**23b**): δ_H 9.10 (1 H, br s, OH, exchanges with D_2O), 6.85 (1 H, t, *J* 4.5 Hz), 2.68—2.58 (2 H, m), 2.45—2.35 (2 H, m), and 2.01 (1 H, t, *J* 2.5 Hz); *m/z* (c.i.) 98 ($M^+ + 1$).

Crystallographic Analysis.—Unit cell parameters and intensity data were obtained by following previously detailed procedures,[24] using a CAD4 diffractometer operating in the ω-2θ scan mode, with graphite monochromated Mo-K_α radiation (λ = 0.71069 Å). The reflection intensities for both structures were corrected for absorption, using the azimuthal-scan method.[25] The relevant experimental data are summarized in Table 2. The structures were solved by the application of routine heavy-atom methods (SHELX84[26]), and refined by full-matrix least-squares (SHELX76[27]). All non-hydrogen atoms were

refined anisotropically. All hydrogen atoms were located and refined isotropically. Atomic scattering factors and anomalous scattering parameters were taken from references 28 to 29 respectively. All computations were made on a DEC VAX-11/750 computer. Atomic co-ordinates for (**8d**)·MeI and (**8e**)·MeI are given in Tables 3 and 5 respectively and bond lengths and angles in Tables 4 and 6. Tables of isotropic hydrogen atom co-ordinates and anisotropic thermal coefficients, are available on request from the Cambridge Crystallographic Data Centre.*

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* For details see 'Instructions for Authors (1989)', *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

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