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N-Alkenyl Nitrone Dipolar Cycloaddition Routes to Piperidines and Indolizidines. Part 8†. The Scope of Tandem Reactions Involving Hydroxylamine-Alkyne Cyclisations

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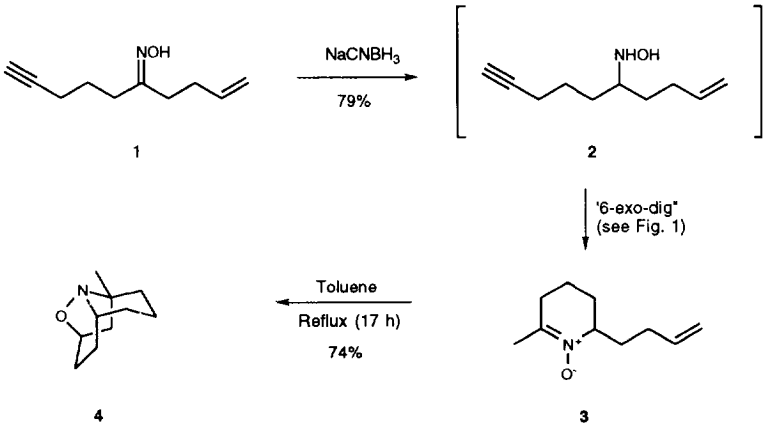
Abstract: A tandem sequence of hydroxylamine-alkyne cyclisation/1,3-dipolar cycloaddition, provides useful entry into tricyclic systems of type **4**. The scope of such reactions is explored in this paper. A novel cascade cyclisation of *N*-hydroxypyrrolidines of type **26** and **28** involving hydroxylamine-alkyne cyclisation, Cope elimination and 1,3-dipolar cycloaddition is also reported. Copyright © 1996 Elsevier Science Ltd

The addition of 'N-O-H' units across carbon-carbon multiple bonds is the reverse of the well known Cope elimination and has been observed for oximes with alkenes,[1-5] allenes,[6-9] alkynes[10-11] and for hydroxylamines with alkenes,[12-18] and alkynes.[19-23] These processes are believed to be concerted processes, and have been termed 1,3-azaprotio transfer (1,3-APT) reactions.[5]

Scheme 1



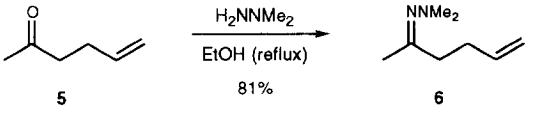
We have shown that hydroxylamine-alkyne cyclisations provide a concise approach to a range of cyclic nitrones.[21-23] Furthermore if a suitably placed double bond is present in the molecule then a subsequent

†Part 7. Reference 23

1,3-dipolar cycloaddition of the resultant nitrone (e.g. **3**) can occur to produce tricycle **4** (Scheme 1).[20] The tricycles (e.g. **3**) could potentially offer access to a range of alkaloids, and we decided to investigate the scope for such hydroxylamine-alkyne cyclisation/1,3-dipolar cycloaddition cascades. A general route was established for the preparation of a range of butenenyl oximes also containing a terminal trimethylsilyl alkyne group separated from the oxime carbon by a variable number of methylene groups.

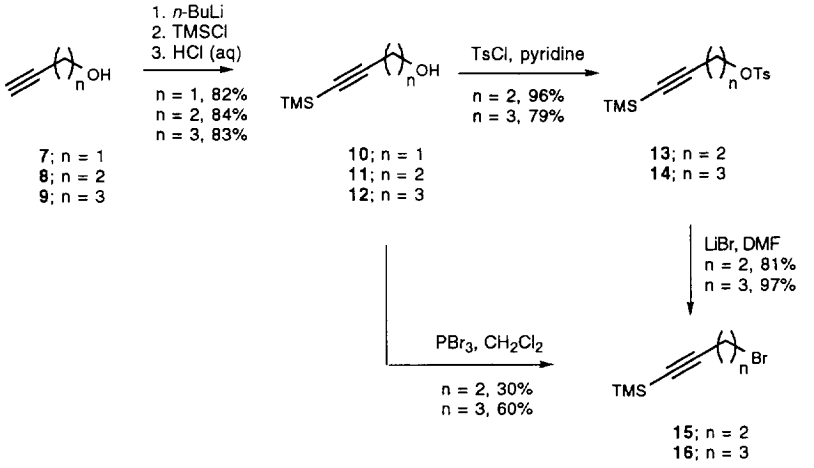
The commercially available 5-hexen-2-one **5** was chosen to provide the butenyl-containing portion of the molecule and was converted into the *N,N*-dimethyl hydrazone **6** (Scheme 2). This guaranteed that kinetic alkylation of the aza-enolate by the alkynyl bromides occurred at the methyl carbon.[24]

Scheme 2



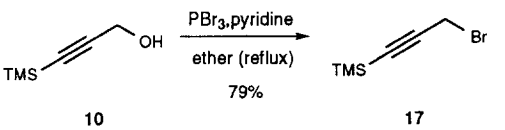
A series of ω-trimethylsilylalkynyl bromides was prepared from the corresponding alkyn-1-ols, firstly by silylation of the terminal alkyne, followed by tosylation and subsequent conversion into the corresponding bromide (Scheme 3).

Scheme 3



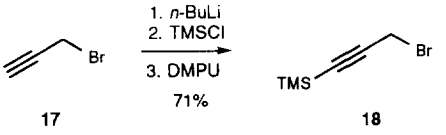
A modified procedure[25] using phosphorus tribromide in refluxing pyridine-ether was used to convert the protected alcohol **10** into the propargyl bromide **17** (Scheme 4).

Scheme 4



The bromide **18** was also prepared in one step from propargyl bromide **17** by direct silylation of the alkyne (Scheme 5).[26]

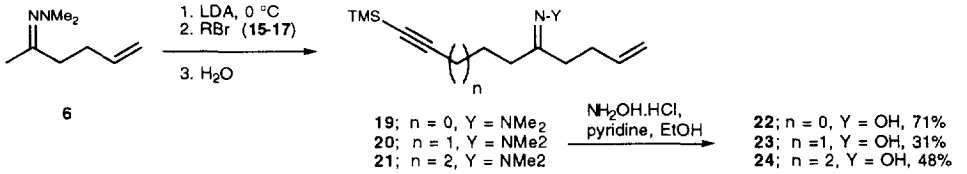
Scheme 5



17 **18**

The aza-enolate derived from **6** was alkylated with the bromo-alkynes using the procedure of Corey and Enders.[24] The hydrazones **19**, **20** and **21** produced were not purified, owing to their ready desilylation on silica.[27] Conversion into the corresponding oximes **22**, **23** and **24** was accomplished using hydroxylamine hydrochloride in pyridine-ethanol. The oximes were isolated as a mixture of *E* and *Z* isomers (Scheme 6).

Scheme 6



6

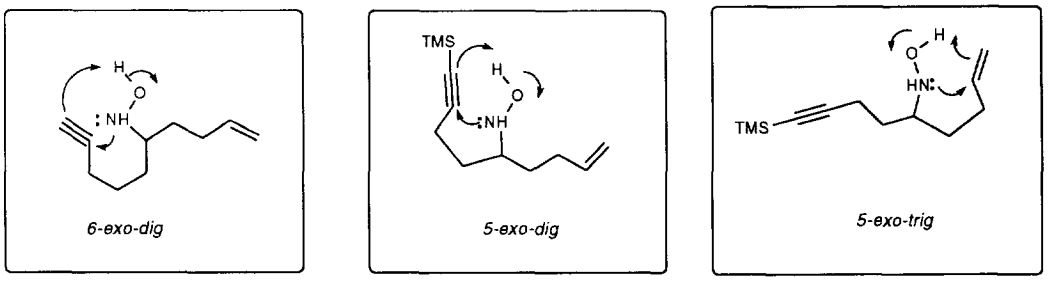
19; n = 0, Y = NMe_2
20; n = 1, Y = NMe2
21; n = 2, Y = NMe2

22; n = 0, Y = OH, 71%
23; n =1, Y = OH, 31%
24; n = 2, Y = OH, 48%

The cyanoborohydride reduction of the oxime **23** with sodium cyanoborohydride in methanol at pH 3-4,[12-13] gave the six-membered nitrone **3** which was thermally converted into the adduct **4** according to the original procedure of Smith.[20]

As shown in Figure 1 we classify the cyclisation mode for **2** to **3** as "6-exo-dig" using Baldwin's terminology,[28] and we similarly classify a cyclisation onto an ω-butynyl (or butenyl) chain as "5-exo dig (trig)" respectively. In our experience the "exo-dig" cyclisations were comparable for a terminal alkyne or the corresponding trimethylsilylated derivative, as the resulting intermediate enaminovinylsilane underwent desilylation after a prototropic shift.[23]

Figure 1

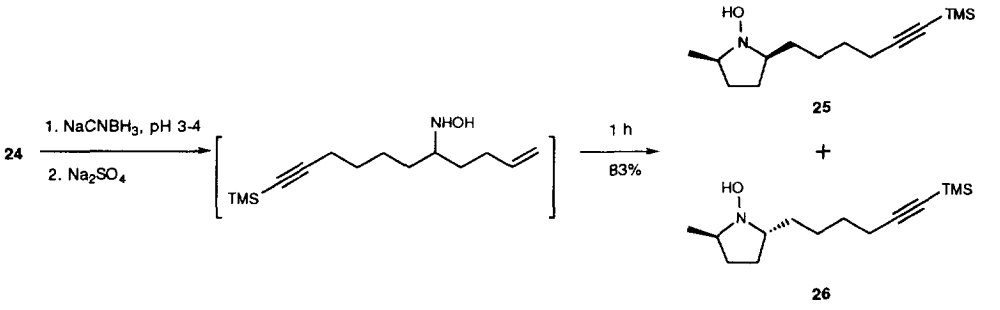


6-exo-dig *5-exo-dig* *5-exo-trig*

It was our intention to examine the related processes for the 5-membered and 7-membered nitrone analogues of **3** and the intramolecular trapping with a butenyl tether. The formation of the 7-membered nitrone would require "7-exo-dig" cyclisation of the hydroxylamine derived from **24** (Scheme 7). However, this

compound underwent a preferential "5-exo-trig" cyclisation[13-18] to give the *N*-hydroxypyrrolidines **25** and **26**, in a ratio of between 1:3 and 1:2.

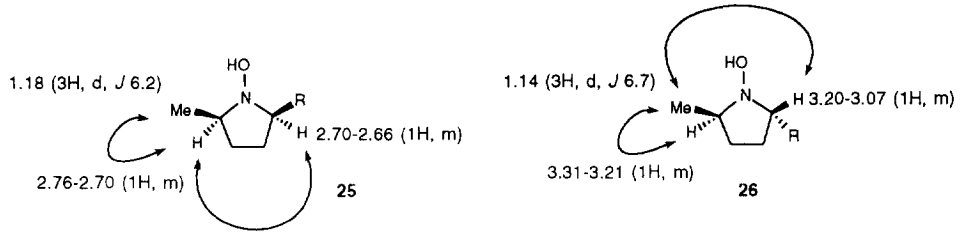
Scheme 7



The *cis*-isomer **25** was confirmed as the less polar product [R*f* 0.16, 8:2 hexane-ethylacetate] by NOEs in the ^{1}H NMR spectrum between (i) both transannular protons adjacent to the nitrogen [δ_H (400 MHz, $CDCl_3$) 2.76-2.70 (1H, m)] and [δ_H (400 MHz, $CDCl_3$) 2.70-2.66 (1H, m)] (ii) the methyl group on the ring [δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.2)] and the adjacent ring proton [δ_H (400 MHz, $CDCl_3$) 2.76-2.70 (1H, m)] (Figure 1).

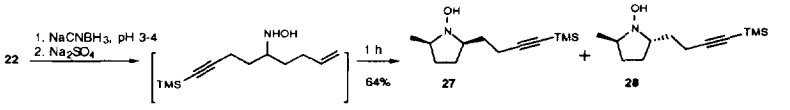
The more polar product [R*f* 0.09, 8:2 hexane-ethylacetate] was assigned as the *trans*-isomer **26** for which NOEs were detected in the ^{1}H NMR spectra between (i) the methyl group on the ring [δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.7)] and the transannular proton adjacent to the nitrogen [δ_H (400 MHz, $CDCl_3$) 3.20-3.07 (1H, m)] (ii) the methyl group on the ring [δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.7)] and the adjacent ring proton [δ_H (400 MHz, $CDCl_3$) 3.31-3.21 (1H, m)]. The reciprocal NOEs were also detected (Figure 2).

Figure 2: NOE Data for the Hydroxylamines **25** and **26** (δ_H values in ppm; *J* values in Hz)



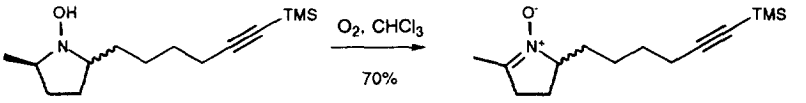
The analogous competition between "5-exo-dig" and "5-exo-trig" cyclisations could be tested using the hydroxylamine derived from the oxime **22** (Scheme 8). This yielded the *N*-hydroxypyrrolidines **27** and **28** in a

Scheme 8



ratio of 1:2. The *N*-hydroxypyrrolidines formed were found to be prone to aereal oxidation, in analogy to results reported for similar compounds by others (Scheme 9).[12, 14]

Scheme 9

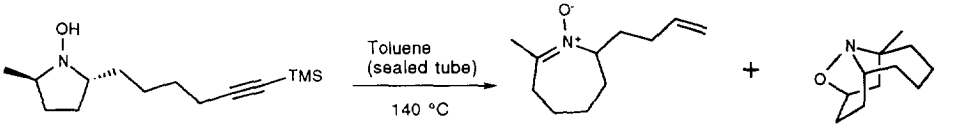


25 / 26 **29**

Rearrangement of the* N-*Hydroxypyrrolidines

Although the required tricyclic adducts were not obtained from **22** and **24** the product *N*-hydroxypyrrolidines offered the opportunity of further hydroxylamine-alkyne cyclisation. The *N*-hydroxypyrrolidine could be regarded as a secondary hydroxylamine which could undergo intramolecular cyclisation with the alkyne function in the same molecule.[17,18] The *cis* and *trans* isomers **25** and **26** were separated. Heating the *trans* isomer **26** in a sealed tube afforded the unexpected tricycle **31** and the cyclic nitrone **30** (Scheme 10).

Scheme 10



26 **30** **31**

The structure of tricycle **31** was assigned using NMR, and also by comparison with the known tricycle **4**.[20] The main features of the ^1H NMR spectrum of compound **31** are the C*H*O signal [δ_H (200 MHz, $CDCl_3$) 4.48-4.43 (1H, m)], the C*H*N signal [δ_H (200 MHz, $CDCl_3$) 3.39 (1H, tt, *J* 8.9, 4.3)] and the ring methyl signal [δ_H (200 MHz, $CDCl_3$) 1.27 (3H, s)]. These compare favourably with the analogous resonances in the known tricycle **4**.[20]

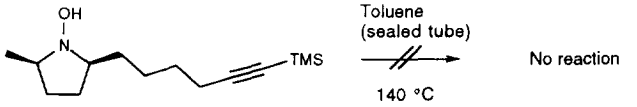
Figure 3

4 **31**

Use of an attached proton test (APT) in the ^{13}C spectrum also shows that the carbon adjacent to the oxygen atom [δ_C (50 MHz, $CDCl_3$) 76.8 (d)] has a doublet multiplicity (CH), which supports the proposed tricyclic structure.

The optimum conditions for formation of **31** were found to be heating in degassed toluene for 23 hours at 140 °C in a sealed tube. Degassed toluene was essential to prevent oxidation of the starting material as reported earlier. The *cis*-isomer **25** was found not to react under the established optimum conditions (Scheme 11).

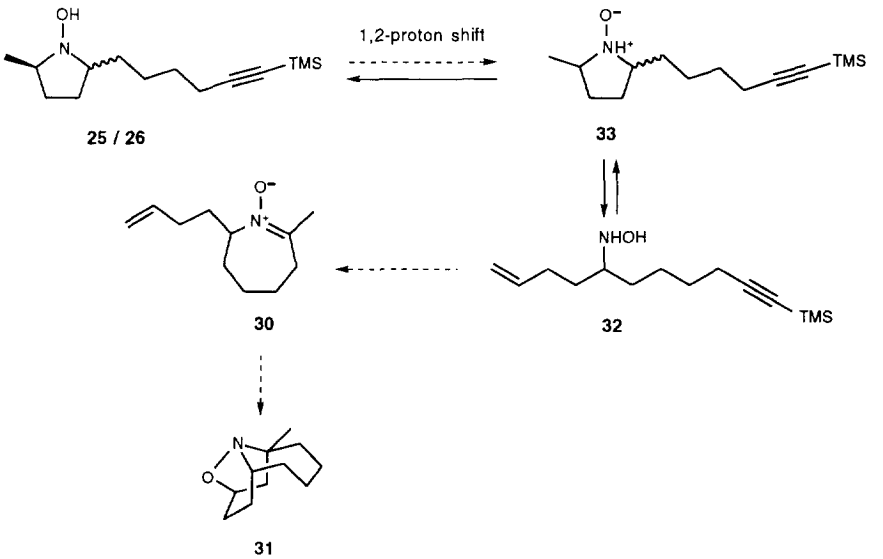
Scheme 11



25

A possible pathway for the conversion of **26** into **31** could involve the re-opening of the *N*-hydroxypyrrolidines followed by "7-exo-dig" closure onto the triple bond, to give the nitrone **30** and hence the tricycle **31** (Scheme 12). We believe that this pathway is unlikely. Although the cyclisation of secondary hydroxylamines with alkenes to give cyclic *N*-oxides (the reverse Cope elimination is known to be reversible,[16-18]) the "5-exo-trig" cyclisation product **33** of a primary hydroxylamine (as in the present work) undergoes a further proton shift to give the *N*-hydroxypyrrolidines **25/26**. Thus the opening of **26** would first require a protrotropic shift to the protonated *N*-oxide **33** before Cope elimination. A further argument against the ring-opening of the hydroxypyrrolidine to an acyclic hydroxylamine is that the *cis*-isomer **25** would also be expected to follow this pathway and it evidently does not (Scheme 11).

Scheme 12

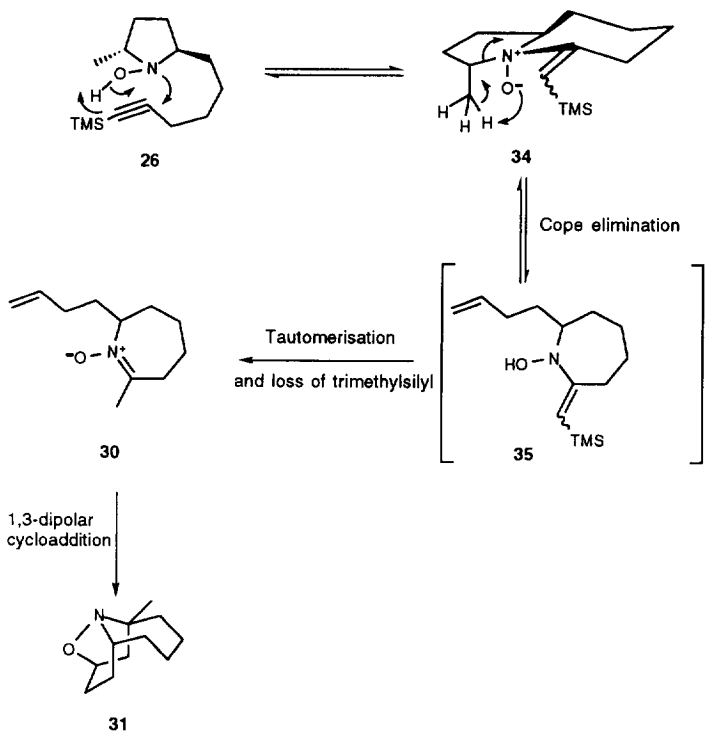


25 / 26 **33** **30** **32** **31**

We therefore propose an alternative cascade mechanism, comprising a hydroxylamine-alkyne cyclisation, Cope elimination and 1,3-dipolar cycloaddition (Scheme 13). Initial intramolecular attack of the

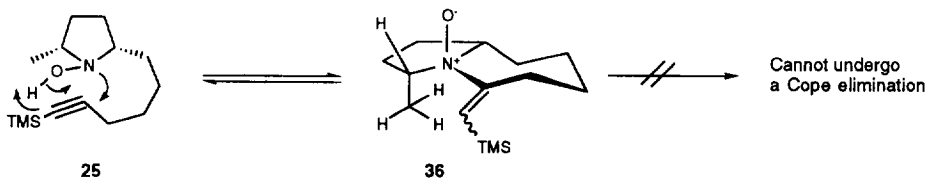
cyclic hydroxylamine onto the triple bond would result in formation of a bicyclic *N*-oxide. The product **34** of the cyclisation of the *trans N*-hydroxypyrrolidine **26**, has the resulting *N*-oxide oxygen *syn* to the α-methyl group. A Cope elimination can thus follow to give **35** which can tautomerise, lose silicon and give the isolated nitrone **30**. This can then undergo an intramolecular 1,3-dipolar cycloaddition onto the double bond to give the product tricycle **31**. Winterfeldt has observed secondary Cope elimination from the *N*-oxides formed by the Michael addition of hydroxylamines to acetylenic esters.[29-30]

Scheme 13



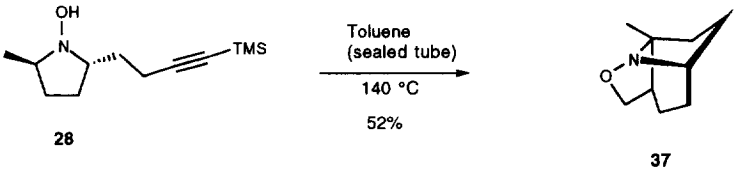
The *cis* isomer **25** could in principle undergo a similar hydroxylamine-alkyne cyclisation, but this would be more sterically hindered (Me *syn* to the approaching alkyne) and the resultant *N*-oxide **36** would have the *N*-oxide oxygen and α-methyl group *anti* to each other, and would thus be incapable of further reaction (Scheme 14).

Scheme 14



The shorter chain *N*-hydroxypyrrolidines **28** should also be capable of following the tandem reaction, and indeed reacted under the optimised conditions previously established to give the tricyclic compound **37** (Scheme 15). The *cis*-isomer **27** did not react (Scheme 16).

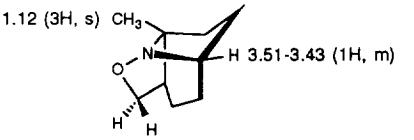
Scheme 15



28 **37**

The structure of the tricycle **37** was assigned from ^{1}H and ^{13}C nmr data and by contrast / comparison with the previously synthesised tricycles **4** and **31**. The C*H*N signal [δ_H (400 MHz, $CDCl_3$) 3.51-3.43 (1H, m)] and CH_3 signal [δ_H (200 MHz, $CDCl_3$) 1.12 (3H, s)] are almost identical to the corresponding peaks of the tricycles **4** and **31** (Figure 4). This indicates that the nitrogen-containing ring of the tricycle is relatively unchanged. However there are two separate signals for two protons on the carbon attached to oxygen [δ_H (400 MHz, $CDCl_3$) 3.95 (1H, d, *J* 6.9) and 4.10-4.05 (1H, m)] indicating that the regioselectivity for the addition of the alkene to the 5-membered cyclic nitrone is reversed from that observed for **4** and **31** (see Figure 5).

Figure 4 Assignment of ^{1}H NMR resonances to the adduct **37**

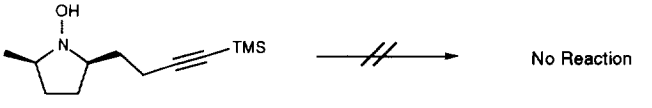


37

(δ_H values in ppm; *J* values in Hz)

This is also supported by a 500 MHz (H-H) COSY NMR spectrum. Use of an attached proton test (APT) in the ^{13}C NMR spectrum also shows a triplet multiplicity (CH_2) for the resonance of the carbon atom adjacent to the oxygen [δ_H (100 MHz, $CDCl_3$) 74.5 (t)].

Scheme 16

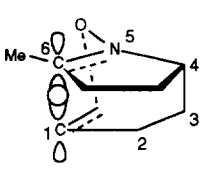


27

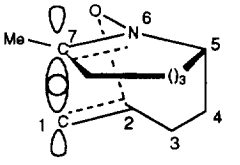
Again these observations can be rationalised by initial hydroxylamine-alkyne cyclisation followed by Cope elimination between the *N*-oxide oxygen and α-methyl group which are *syn* to each other. For the "5-exo-dig" product from *cis* isomer **27** the *N*-oxide oxygen and α-methyl group are again *anti* to each other, and are thus unreactive (Scheme 16).

All the evidence points to the opposite regiochemistry of addition for the 1,3-dipolar cycloaddition of the proposed precursor 5-membered nitrone, to that observed for the 6- and 7-membered cyclic nitrones **3** and **30**. The different regiochemistry of the 1,3-dipolar cycloaddition of the nitrone intermediates can be rationalised proposing a kinetically preferred cycloaddition (C-C bond leads C-O bond formation and occurs to produce the kinetically preferred ring size) for the 5-membered cyclic nitrone.[31-32] The larger ring sizes however constrain the cycloaddition to occur such that the nitrone oxygen attacks the non-terminal end of the double bond (Figure 5).

Figure 5



C-C attack kinetically preferred in smaller ring

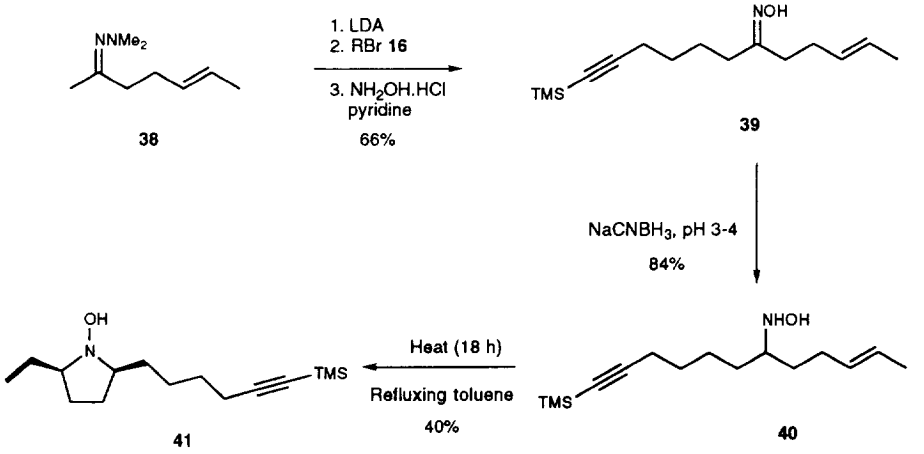


O attack at non-terminal end

Steric Blocking of Hydroxylamine Cyclisation onto the Double Bond

As "5-exo-trig" cyclisation of the hydroxylamines onto the double bond had been preferred over cyclisation onto the triple bond in all but the "6-exo-dig" case, the obvious step was to attempt to block this competing reaction. Steric blocking of the terminal position of alkenes had been shown by Black[14] and Ciganek[16] to slow intramolecular cyclisation with hydroxylamines. Thus initially we chose to block the terminal position of the double bond with a methyl group. Alkylation of the aza-enolate of the N,N-dimethylhydrazone of 5-hepten-2-one with the bromide **16**, followed by reaction with hydroxylamine hydrochloride in pyridine provided the oxime **39**. Reduction under the usual conditions ($NaCNBH_3$ / MeOH / pH 3-4) gave the isolable

Scheme 17

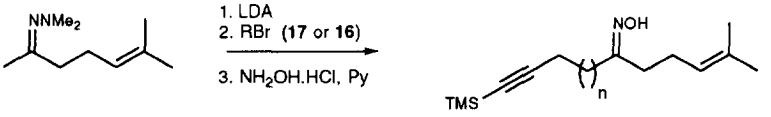


hydroxylamine **40**. On heating in refluxing toluene the corresponding *N*-hydroxypyrrolidine **41** was isolated, indicating a continuing preference for "5-exo-trig" cyclisation (Scheme 17).

Only the *cis*-isomer **41** was isolated from the reaction mixture. Perhaps the *trans*-isomer was consumed by undergoing a further hydroxylamine-alkyne cyclisation and rearrangement as reported earlier. However none of the expected tricycle or nitrone products was isolated. The *cis*-isomer would be produced and isolated as it would not undergo further reaction.

We therefore decided to block the terminal alkene position with two methyl groups. Readily available 6-methyl-5-hepten-2-one was protected as the *N,N*-dimethylhydrazone **42**. Alkylation with lithium diisopropylamide and either the bromides **17** or **16**, under the usual conditions gave the oximes **43** and **44** respectively, after treatment with hydroxylamine hydrochloride/pyridine (Scheme 18).

Scheme 18

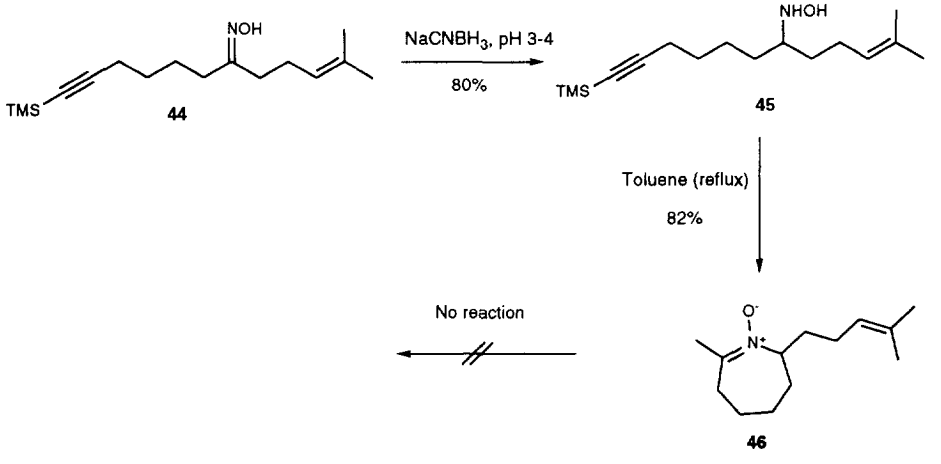


42

43; n = 1 (64%)
44; n = 3 (74%)

Reduction of the oxime **44** with sodium cyanoborohydride gave the isolable hydroxylamine **45**. On being heated in refluxing toluene this formed the required cyclic nitrone **46** by "7-exo-dig" hydroxylamine-alkyne cyclisation (Scheme 19).

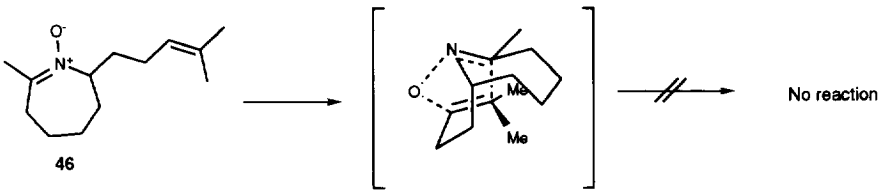
Scheme 19



44 **45** **46**

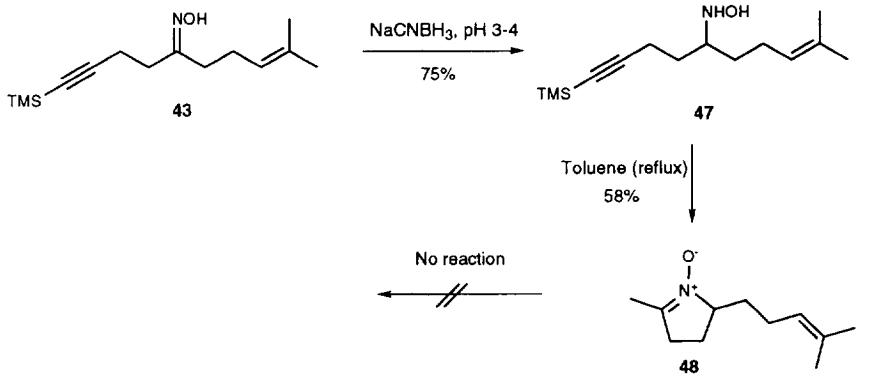
The nitrone **46** failed under a variety of conditions to undergo a further 1,3-dipolar cycloaddition, probably for steric reasons. Cycloaddition would involve the formation of adjacent quaternary centres, which may be unfavoured (Scheme 20).

Scheme 20



Similarly the oxime **43** was reduced to the hydroxylamine **47**. Again this cyclised smoothly via a "5-exo-dig" mode onto the triple bond to give the cyclic nitrone **48**. Further cycloaddition was unsuccessful, presumably owing to the steric problems encountered earlier (Scheme 21).

Scheme 21



Conclusion

The "5-exo-trig" mode of hydroxylamine cyclisation is kinetically preferred over the "5-" and "7-exo-dig" mode, but not the "6-exo-dig" mode. However, dimethyl substitution of the terminal alkene can suppress the "5-exo-trig" mode and therefore permit the alternative "exo-dig" cyclisations. In these cases the resultant dipolarophiles appear too sterically hindered to add to the intermediate cyclic nitrones. A new cascade reaction of alkyne-containing *N*-hydroxypyrrolidines has been discovered, involving hydroxylamine-alkyne cyclisation, Cope elimination and 1,3-dipolar cycloaddition, leading eventually to the required intermediate 5- and 7-membered cyclic nitrones for intramolecular 1,3-dipolar trapping by the pendant butenyl dipolarophiles.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian EM-390 (90 MHz), Bruker AC-200 (200 MHz), Bruker WM-250 (250 MHz), JEOL JX-270 (270 MHz), Bruker AM-400 (400 MHz) or Bruker DRX-500 (500 MHz) instruments. Chemical shifts are measured in ppm relative to TMS ($\delta = 0$) using $CDCl_3$ or C_6D_6 as internal standard. *J* values are given in Hz. Attached Proton Tests (APT) were used to help distinguish between C (s), CH (d), CH_2 (t), CH_3 (q) groups. Infrared spectra were recorded on a Perkin-Elmer 1310 or on a Perkin-Elmer 1600 series FTIR spectrophotometer. The relative intensities of absorption are indicated as: s,

strong; m, medium; w, weak; br, broad. Mass spectra were recorded by the Mass Spectrometry Services of the University of Swansea, the University of Cambridge or SmithKline Beecham Pharmaceuticals, Harlow. Analytical thin layer chromatography (TLC) was carried out on Merck precoated 0.25 mm thick plates Kieselgel 60 F_{254}. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Microanalyses were carried out either by the Microanalytical Services at the University of Cambridge or at SmithKline Beecham Pharmaceuticals, Harlow. As some of the intermediates in this synthesis were unstable oils which did not give satisfactory microanalysis data, either TLC or gas chromatography (GC) was used as an indicator of sample purity. Melting points were determined using a Büchi 510 melting point apparatus and are uncorrected. THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator. Other dry solvents were purified by standard techniques.[33] Petroleum ether (pet. ether) refers to the fraction b.p. 40-60 °C. Brine refers to a saturated solution of sodium chloride in water.

5-Hexen-2-one dimethylhydrazone **6**

The procedure reported for 2-pentanone was followed.[20] To a solution of 5-hexen-2-one (10 g, 102 mmol) in dry ethanol (25 cm^3) was added *N,N*-dimethyl hydrazone (23 cm^3, 300 mmol). The solution was gently refluxed for 2 hours. The solution was evaporated *in vacuo* to remove excess *N,N*-dimethyl hydrazone and ethanol. The residue was distilled under reduced pressure to give the *hydrazone* **6** (11.6 g, 81%) as a colourless liquid; b.p. 72-74 °C at 12 mm Hg; ν_{max} (thin film)/cm^{-1} 3080m (C=CH), 1641s (C=N); δ_H (250 MHz, $CDCl_3$) mixture of geometric isomers 5.85-5.69 (1H, m, C*H*=CH_2), 5.07-4.90 (2H, m, CH=CH_2), 2.36 and 2.33 (6H, 2 x s, NNMe_2), 2.22 and 2.21 (4H, 2 x s, CH_2CH_2), 1.89-1.88 (3H, 2 x s, CH_3); δ_C (63 MHz, $CDCl_3$) 167.1 (s), 137.6 (d), 115.2 (t), 47.6 (q), 47.2 (q), 38.3 (t), 31.2 (t), 16.8 (q).

3-Trimethylsilyl-2-propyn-1-ol **10**[34]

n-Butyllithium (1.5M in hexane, 150 cm^3, 226 mmol) was added dropwise to a stirred solution of 2-propyn-1-ol (5.74 g, 102 mmol) in THF (300 cm^3) at -78 °C under nitrogen. After 20 minutes chlorotrimethylsilane (39 cm^3, 307 mmol) was added dropwise at -78 °C under nitrogen. The solution was allowed to warm to 20 °C, and aqueous hydrochloric acid (2M, 200 cm^3) was added. After 16 hours the layers were separated and the aqueous layer extracted with ether (2 x 200 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (silica, eluting with hexane then ether) and distillation under reduced pressure, to give pure *alcohol* **10** (10.7 g, 82 %) as a pale yellow oil. b.p. 95-96 °C at 22 mmHg (lit.,[34] 76 °C at 11 mmHg); R_f 0.43, 1:1 hexane-ether; ν_{max} (thin film)/cm^{-1} (CCl_4) 3620s (O-H), 3497m (O-H), 2176s (C≡C); δ_H (90 MHz, $CDCl_3$) 4.25 (2H, s, CH_2OH), 0.20 (9H, s, (CH_3)$_3$Si); δ_C (63 MHz, $CDCl_3$) 103.7 (s), 90.7 (s), 51.6 (t), 0.2 (q).

3-Bromo-1-trimethylsilyl-1-propyne **17**[25]

(i) Alcohol **10** (8 g, 62.5 mmol) was dissolved in pyridine (0.13 cm^3) and dry ether (32 cm^3). Phosphorus tribromide (2.4 cm^3) in ether (10 cm^3) was added and the solution refluxed for 3 hours. The mixture was poured into ice and the aqueous layers extracted with ether (3 x 50 cm^3). The combined organic layers were washed with water, saturated sodium hydrogen carbonate solution and saturated aqueous ammonium chloride solution. The organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by distillation under reduced pressure using a Vigreux column gave the *bromide* **17** (1.34 g, 79 %) as a colourless liquid; b.p. 63-64 °C at 18 mm Hg (lit.,[25] 62-63 °C at 3 mm Hg); R_f 0.64, 1:1 hexane-ethyl acetate; ν_{max} (CCl_4)/cm^{-1} 2178s (C≡C); δ_H (200 MHz, $CDCl_3$) 3.91 (2H, s, CH_2Br), 0.15 (9H, s, (CH_3)$_2$Si-); δ_C (100 MHz, $CDCl_3$) 99.9 (s), 92.3 (s), 14.7 (t), 0.0 (q).

(ii) To a stirred solution of propargyl bromide (80% wt. in toluene, 6.55 cm^3, 0.06 mmol) in ether (60 cm^3) and hexane (20 cm^3) was added *n*-butyllithium (1.5M in hexane, 39 cm^3, 0.06 mmol) dropwise at -78 °C under argon. After 1 hour chlorotrimethylsilane (15.2 cm^3, 0.12 mmol) was added, followed by DMPU (10 cm^3) dropwise at -78 °C under argon, and the solution slowly warmed to 10 °C. The white suspension was poured into aqueous hydrochloric acid (2M, 120 cm^3) and extracted with ether (4 x 100cm^3). The combined organic layers were dried ($MgSO_4$) and purified by distillation under reduced pressure, to give the *bromide* **17** (8.1 g, 71%) as a colourless liquid.

4-Trimethylsilyl-3-butyn-1-ol **11**[35]

n-Butyllithium (1.5M in hexane, 105 cm^3, 158 mmol) was added dropwise to a stirred solution of 3-butyn-1-ol (5 g, 71.4 mmol) in THF (400 cm^3) at -78 °C under nitrogen. After 30 minutes chlorotrimethylsilane (27.2 cm^3, 214 mmol) was added dropwise at -78 °C under nitrogen. The solution was allowed to warm to 20 °C, and quenched with aqueous hydrochloric acid (2M, 100 cm^3). After 60 hours the layers were separated and the aqueous layer extracted with ether (2 x 200 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (silica, eluting with hexane followed by ether) and distillation, to give pure *alcohol* **11** (8.5 g, 84%) as a colourless liquid; b.p. 97-98 °C at 24 mm Hg (lit.,[35] 72 °C, 12 mm Hg); R_f 0.25, 1:1 hexane-ether; ν_{max} (thin film)/cm^{-1} 3330s (O-H), 2177s (C≡C); δ_H (250 MHz, $CDCl_3$) 3.68 (2H, t, *J* 6.3, CH_2OH), 2.47 (2H, t, *J* 6.3, $CH_2C{\equiv}C$), 0.13 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 103.5 (s), 87.1 (s), 61.0 (t), 29.8 (t), 0.19 (q).

(4-Trimethylsilyl-3-butyn-1-yl)-4-toluene sulphonate **13**[35]

4-Toluenesulphonyl chloride (23.6g, 124 mmol) was added to a stirred solution of the alcohol **11** (16 g, 112 mmol) in pyridine (75 cm^3) at 0 °C under nitrogen. After 10 hours, saturated aqueous sodium hydrogen carbonate solution (100 cm^3) was added and the solution stirred at 20 °C for 30 minutes. The mixture was poured into saturated aqueous sodium hydrogen carbonate (200 cm^3), and the mixture extracted with ether (3 x 200 cm^3). The combined organic layers were washed with saturated aqueous copper (II) sulfate solution and dried ($MgSO_4$).

The solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 8:2 hexane-ether). Pure *tosylate* **13** (32 g, 96%) was isolated as a colourless oil; R_f 0.37, 8:2 hexane-ether; ν_{max} (CCl_4)/cm^{-1} 2181s (C≡C), 1599m (Ar, C=C); δ_H (90 MHz, $CDCl_3$) 7.80 (2H, d, *J* 9.0, $CHCSO_3$), 7.34 (2H, d, *J* 9.0, $CHCCH_3$), 4.10 (2H, t, *J* 7.72, CH_2O), 2.58 (2H, t, *J* 7.2, $CH_2C{\equiv}C$), 2.45 (3H, s, CH_3C), 0.11 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 144.9 (s), 132.9 (s), 129.9 (d), 127.9 (d), 100.3 (s), 87.4 (s), 67.5 (t), 21.6 (t), 20.7 (q), 0.1 (q).

4-Bromo-1-Trimethylsilyl-1-butyne **15**[35]

(i) A stirred solution of the tosylate **13** (30 g, 101 mmol) and lithium bromide (9.64 g, 118 mmol) in dry DMF (150 cm^3) was heated to 50 °C under nitrogen for 3 hours. The solution was poured into water and the mixture was extracted with hexane (3 x 200 cm^3). The organic layers were washed with water (4 x 200 cm^3), combined and dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by distillation under reduced pressure, using a Vigreux column, to give pure *bromide* **15** (17.5 g, 83%) as a colourless liquid; b.p. 74-76 °C at 20 mm Hg; R_f 0.62, 9:1 hexane-ethyl acetate; ν_{max} (CCl_4)/cm^{-1} 2177s (C≡C); δ_H (90 MHz, $CDCl_3$) 3.28 (2H, t, *J* 7.5, CH_2Br), 2.60 (2H, t, *J* 7.5, $CH_2C{\equiv}C$), 0.10 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 103.2 (s), 87.0 (s), 29.2 (t), 24.3 (t), 0.0 (q).

(ii) 4-Trimethylsilyl-3-butyn-1-ol **11** (2 g, 14 mmol) was dissolved in dry dichloromethane (40 cm^3). To this solution was added phosphorus tribromide (0.67 cm^3, 7 mmol) at 0 °C under nitrogen. The mixture was stirred for 15 minutes, and methanol (1.7 cm^3) carefully added at 0 °C. The mixture was diluted with dichloromethane (20 cm^3) and water (15 cm^3) was added. The layers were separated, and the aqueous layer extracted with dichloromethane (3 x 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (silica, eluting 1:1 hexane-ether) to give pure *bromide* **15** (0.92 g, 32 %) as colourless liquid and starting alcohol (0.97 g).

5-Trimethylsilyl-4-pentyn-1-ol **12**

n-Butyllithium (1.5M in hexane, 53 cm^3, 2.2 equiv., 78.8 mmol) was added dropwise to a stirred solution of 4-pentyn-1-ol (3 g, 35.6 mmol) in dry THF (150 cm^3) at -78 °C under nitrogen. After 10 minutes chlorotrimethylsilane (13.6 cm^3, 107 mmol) was added dropwise at -78 °C under nitrogen. The solution was allowed to warm to 20 °C and quenched with aqueous hydrochloric acid (2M, 70 cm^3). After 48 hours the layers were separated, and the aqueous layer extracted with ether (2 x 40 cm^3). The combined organic layers were dried ($MgSO_4$), and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (silica, eluting with hexane followed by ether), and distillation under reduced pressure. The *silylated alcohol* **12** (4.6 g, 83%) was obtained as a colourless oil; b.p. 118-120 °C at 22 mm Hg (lit.,[36] 47-49 °C at 0.5 mm Hg); R_f 0.25, 1:1 ether-hexane; ν_{max} (thin film)/cm^{-1} 3500-3200br s (O-H), 2180s (C≡C); δ_H (250 MHz, $CDCl_3$) 3.74 (2H, t, *J* 6.1, CH_2OH), 2.33 (2H, t, *J* 6.9, $CH_2C{\equiv}C$), 1.75 (2H, quintet, *J* 6.6, $CH_2CH_2CH_2$), 0.11 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 106.8 (s), 85.5 (s), 62.0 (t), 31.3 (t), 16.7 (t), 0.2 (q).

(5-Trimethylsilyl-4-pentyn-1-yl)-4-toluene sulphonate **14**

4-Toluenesulphonyl chloride (5.3 g, 28 mmol) was added to a stirred solution of 5-trimethylsilyl-4-pentyn-1-ol **12** (1.5 g, 9.8 mmol) in pyridine (10 cm^3) at 0 °C under nitrogen. After 12 hours, saturated aqueous sodium hydrogen carbonate solution (10 cm^3) was added and the suspension stirred for 30 minutes at 20 °C. The mixture was poured into saturated aqueous sodium hydrogen carbonate solution (20 cm^3) and extracted with ether (3 x 20 cm^3). The combined organic layers were washed with copper (II) sulfate solution, dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (silica, eluting 8:2 hexane-ether) to give the *tosylate* **14** (2.34 g, 79%) as a white solid; m.p. 51.5-52 °C; R_f 0.55, 1:1 ether-hexane; ν_{max} (CCl_4)/cm^{-1} 2177s (C≡C), 1600m (Ar, C=C); δ_H (90 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.0, $CHCSO_3$), 7.35 (2H, d, *J* 8.0, CH_3CCH), 4.10 (2H, t, *J* 6.0, CH_2O), 2.40 (3H, s, CH_3), 2.30 (2H, t, *J* 7.0, $CH_2C{\equiv}C$), 1.80 (2H, quintet, *J* 6.5, $CH_2CH_2CH_2$), 0.10 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 144.7 (d), 133.1 (d), 129.9 (s), 127.8 (s), 104.9 (s), 85.8 (s), 70.0 (t), 27.8 (t), 21.6 (q), 16.0 (t), 0.0 (q).

5-Bromo-1-trimethylsilyl-1-pentyne **16**

(i) Lithium bromide (0.31 g, 3.6 mmol) was added to a stirred solution of the tosylate **14** (1 g, 3.23 mmol) in DMF (5 cm^3). The solution was heated to 50 °C for 3 hours. The solution was poured into water (15 cm^3) and extracted with hexane (3 x 20 cm^3). The combined organic layers were washed with water (3 x 20 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the product purified by distillation under reduced pressure, using a Vigreux column, to give the *bromide* **16** (0.69 g, 97%) as a colourless liquid; b.p. 64-66 °C at 4 mm Hg; R_f 0.64, 1:1 hexane-ethyl acetate; ν_{max} (CCl_4)/cm^{-1} 2178s (C≡C); δ_H (250 MHz, $CDCl_3$) 3.51 (2H, t, *J* 6.5, CH_2Br), 2.41 (2H, t, *J* 6.7, $CH_2C{\equiv}C$), 2.04 (2H, quintet, *J* 6.6, $CH_2CH_2CH_2$); δ_C (63 MHz, $CDCl_3$) 104.9 (s), 85.7 (s), 32.2 (t), 31.4 (t), 18.5 (t), 0.0 (q) .

(ii) Phosphorus tribromide (0.7 cm^3, 7 mmol) was added dropwise at 0 °C under nitrogen to a stirred solution of alcohol **12** (2 g, 13 mmol) in dry dichloromethane (40 cm^3). The solution was stirred for 40 minutes and methanol (1.7 cm^3) carefully added. The solution was diluted with dichloromethane (20 cm^3), and water (5 cm^3) added. The layers were separated and the aqueous layer extracted with dichloromethane (3 x 5 cm^3). The organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure (no heat). The compound was purified by distillation using a Vigreux column to give pure *bromide* **16** (1.7 g, 60%), and starting material (0.6 g).

10-Trimethylsilyl-1-decen-9-yn-5-one oxime **23**

n-Butyllithium (1.5M in hexane, 3.68 cm^3, 5.6 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.8 cm^3, 5.68 mmol) in dry THF (10 cm^3) at 0 °C under nitrogen according to the general procedure reported.[20] After 10 minutes 5-hexen-2-one dimethylhydrazone **6** (0.96 mg, 6.8 mmol) was added dropwise at 0 °C under nitrogen. The solution was stirred for 2 hours at 0 °C, and 4-bromo-1-trimethylsilyl-1-butyne **15** (760 g, 3.7 mmol) was added dropwise at 0 °C under nitrogen. After 30 minutes the reaction was allowed to warm to 20 °C, and stirred for a further 12 hours. The reaction was quenched with water (4 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 4 cm^3), and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude *hydrazone* was isolated as a pale yellow oil; δ_H (200 MHz, $CDCl_3$) 5.81 (1H, m, C*H*=CH_2), 5.03 (2H, m, CH=C*H*$_2$), 2.38 (6H, s, (CH_3)$_2$N), 2.37-2.10 (10H, m, -CH_2-), 0.31 (9H, m, (CH_3)$_3$Si)

After removal of the solvent under reduced pressure, pyridine-ethanol (20 cm^3, 1:1) and hydroxylamine hydrochloride (0.8 g, 11.2 mmol) were added and the solution stirred at 20 °C for 2 hours. The solution was poured into aqueous hydrochloric acid (2M, 20 cm^3) and extracted with dichloromethane (3 x 20 cm^3). The combined organic layers were washed with aqueous copper (II) sulfate solution and dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 8:2 hexane-ether) to give pure *oxime* **23** (0.27 g, 31%) as a colourless oil, a mixture of *E* and *Z* oximes. R_f 0.22, 8:2 hexane-ether; [Found: C, 66.0; H, 9.8; N, 5.9%. $C_{13}H_{23}NOSi$ requires C, 65.8; H, 9.8; N, 5.9%]; ν_{max} (thin film)/cm^{-1} 3600m (OH), 3400-3250brs (OH), 2170s (C≡C), 1640m (C=C); δ_H (400 MHz, $CDCl_3$) 9.33 (1H, br s, C=N-O*H*), 5.86-5.76 (1H, m, C*H*=CH_2), 5.09-5.07, 5.03-5.00, 4.97-4.96 (2H, 3 x m, CH=C*H*$_2$), 2.47-2.40 (2H, m), 2.30-2.14 (6H, m), 1.81-1.70 (2H, m), 0.12 (9H, s, (CH_3)$_3$Si); δ_C (100 MHz, $CDCl_3$) 160.2 (s), 137.5 (d), 137.4 (d), 115.4 (t), 115.2 (t), 106.6 (s), 106.5 (s), 85.2 (s), 33.7 (t), 33.0 (t), 30.3 (t), 29.6 (t), 27.1 (t), 26.9 (t), 25.1 (t), 24.7 (t), 20.0 (t), 19.4 (t), 0.1 (q); *m/z* (CI) 238 (MH^+, 26%), 222 (65), 134 (22), 90 (24), 72 (31), 58 (29), 44 (100); [Found: MH^+ 238.1627 (CI). $C_{13}H_{24}NOSi$ requires *MH* 238.1627].

2-(3-Butenyl)-6-methyl-2,3,4,5-tetrahydropyridine-1-oxide **3**[20]

A stirred solution of 10-trimethylsilyl-1-decen-9-yn-5-one oxime **23** (80 mg, 0.34 mmol) in methanol (8 cm^3) was cooled to -10 °C under nitrogen. Sodium cyanoborohydride (43 mg, 0.68 mmol) and methyl orange indicator solution (2 drops) were added. The solution was stirred at -10 °C under nitrogen, and aqueous hydrochloric acid (6M in methanol) was added dropwise so as to just keep the solution pink. After 30 minutes the solution was neutralised with 20% sodium hydroxide solution and the suspension poured into brine (7 cm^3) containing ice.

The suspension was extracted with dichloromethane (4 x 10 cm^3) and the organic extracts were combined and stirred over sodium sulphate for 1 hour at 20 °C. The solution was filtered and the solvent removed under

reduced pressure. The compound was purified by flash column chromatography (silica, eluting 9:1 ethylacetate-methanol) to give the *nitrone* **3** as a colourless oil (50 mg, 88%); R_f 0.08, 9:1, Ethylacetate-methanol; δ_H (400 MHz, $CDCl_3$) 5.77-5.87 (1H, m, C*H*=CH_2), 5.08-4.96 (2H, m, CH=C*H*$_2$), 3.74-3.72 (1H, m, C*H*N$^+$), 2.43-2.36 (2H, m, C*H*$_2$C=N$^+$), 2.18-2.10 (2H, m, CH_2CH=CH_2), 2.08 (3H, s, C*H*$_3$), 1.94-1.20 (6H, m); δ_C (63 MHz, $CDCl_3$) 145.4 (s), 137.4 (d), 115.2 (t), 66.2 (d), 31.4 (t), 30.8 (t), 30.4 (t), 26.6 (t), 18.4 (q), 15.6 (t).

*(3*R**, 6*R**, 10*S**)-10-Methyl-2-oxa-1-azatricyclo[4,4,1^{3,10}.0]undecane* **4**[20]

A solution of nitrone **3** (15 mg, 0.1 mmol) in dry toluene (8 cm^3) was refluxed under argon, under Dean-Stark conditions for 17 hours. The solvent was removed under reduced pressure, and the compound was purified by flash column chromatography (silica, eluting 1:1 hexane-ether) to give the *isoxazolidine* **4** (11 mg, 73 %) as an off-white solid. This was converted to the *hydrochloride salt*; m.p. 211-212 °C (decomp.); [Found: C, 58.9; H, 9.0; N, 6.8%. $C_{10}H_{18}ClNO$ requires C, 59.1; H, 8.9; N, 6.9%]; ν_{max} (CCl_4)/cm^{-1} no stretches other than C-H above 1500; δ_H (250 MHz, $CDCl_3$) 4.83-4.80 (1H, m, C*H*O), 4.02-3.97 (1H, m, C*H*N), 2.50-1.57 (12H, m), 1.55 (3H, s, -C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 77.0 (d), 69.4 (s), 55.8 (d), 39.0 (t), 32.6 (t), 28.5 (q), 27.0 (t), 18.4 (t), 13.6 (t); *m/z* (EI) 167 (M^+, 8%), 113 (24), 96 (100), 55 (32), 41 (44); [Found: M^+ 167.1310 (EI). $C_{10}H_{17}NO$ requires *M* 167.1310].

11-Trimethylsilyl-1-undec-10-yn-5-one oxime **24**

n-Butyllithium (1.5M in hexane, 1.84 cm^3, 2.8 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.4 cm^3, 2.8 mmol) in dry THF (10 cm^3) at 0 °C under nitrogen. After 10 minutes 5-hexen-2-one dimethylhydrazone **6** (0.48 g, 3.4 mmol) was added dropwise at 0 °C under nitrogen. After 2 hours 5-bromo-1-trimethylsilyl-1-pentyne **16** (300 mg, 1.37 mmol) was added dropwise at 0 °C under nitrogen. After 30 minutes the reaction was quenched with water (4 cm^3), the layers separated and the aqueous layer extracted with dichloromethane (2 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude *hydrazone* was isolated as a pale yellow oil. After solvent removal, pyridine-ethanol (10 cm^3, 1:1) and hydroxylamine hydrochloride (0.4 g, 5.6 mmol) were added and the solution stirred at 20 °C for 2 hours. The solution was poured into aqueous hydrochloric acid (2M, 10 cm^3), and the mixture extracted with dichloromethane (3 x 10 cm^3). The organic layers were combined and washed with aqueous copper (II) sulphate solution. The organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica, eluting 8:2 hexane-ether) to give pure *oxime* **24** (163 mg, 48%) as a pale yellow oil, as a mixture of *E* and *Z* isomers; R_f 0.50 and 0.39, 1:1 hexane-ether; [Found: C 67.0; H 10.0; N 5.7%. $C_{14}H_{25}NOSi$ requires C, 66.9, H 10.0, N 5.6%]; ν_{max} (CCl_4)/cm^{-1} 3604s (OH), 3277brm (OH), 3081m (=CH), 2173s (C≡C), 1642m (C=C); δ_H (200 MHz, $CDCl_3$) 9.49 (1H, br s C=N-O*H*), 5.85-5.72 (1H, m, C*H*=CH_2), 5.00-4.95 (2H, 3 x m, CH=C*H*$_2$), 2.47-2.16 (10H, m), 1.78-1.51 (3H, m), 0.12 (9H, s, (CH_3)$_3$Si); δ_C (63 MHz, $CDCl_3$) 160.5 (s), 137.4 (d), 137.2 (d), 115.2 (t), 115.1 (t), 106.9 (s), 84.6 (s), 36.9 (t), 33.4 (t), 33.2 (t), 30.2 (t), 29.4 (t), 27.9 (t), 26.9 (t), 26.7 (t), 25.0 (t), 24.4 (t), 19.5 (t), 19.4 (t), 0.0 (q); *m/z* (EI) 96 (25%), 82 (28), 73 (100), 65 (67); *m/z* (CI) 252 (MH^+, 100%), 236 (50); [Found: MH^+ 252.1784 (CI). $C_{14}H_{25}NOSi$ requires *MH* 252.1784]

*(2*R**, 5*S**)-1-Hydroxy-2-methyl-4-(6'-trimethylsilyl-5'-hexynyl)pyrrolidine* **25** and *(2*R**, 5*R**)-1-Hydroxy-2-methyl-4-(6'-trimethylsilyl-5'-hexynyl)pyrrolidine* **26**

A stirred solution of 11-trimethylsilyl-1-undec-10-yn-5-one oxime **24** (40 mg, 0.16 mmol) in methanol (3 cm^3) was cooled to -10 °C under nitrogen. Sodium cyanoborohydride (20 mg , 0.32 mmol) and methyl orange indicator (2 drops) were added. The solution was stirred at -10 °C under nitrogen, and hydrochloric acid (10M

in methanol) was added dropwise so as to just keep the solution pink. After 30 minutes the solution was made strongly basic with 20% aqueous sodium hydroxide solution and poured into saturated brine (7 cm^3) containing ice. The suspension was extracted with dichloromethane (4 x 7 cm^3) and the organic extracts were combined and stirred over sodium sulphate for 1 hour at 20 °C. The solution was filtered, the solvent removed under reduced pressure and the crude products purified by flash column chromatography (silica, 8:2 eluting hexane-ethyl acetate) to give the cis-*pyrrolidine* **25** (15 mg, 38 %) as a colourless oil; R_f 0.16, 8:2 hexane-ethyl acetate; [Found: C, 66.3; H, 10.7; N, 5.3%. $C_{14}H_{27}NOSi$ requires C, 66.3; H, 10.6; N, 5.5%]; ν_{max} (thin film)/cm^{-1} 3281brm (O-H), 2174s (C≡C); δ_H (400 MHz, $CDCl_3$) 2.76-2.70 (1H, m, CH_3CHN), 2.70-2.66 (1H, m, CH_2CHN), 2.21 (2H, t, *J* 7.0, $CH_2C{\equiv}C$), 1.69-1.62 (2H, m), 1.55-1.49 (2H, m), 1.44-1.27 (6H, m), 1.18 (3H, d, *J* 6.2, CH_3), 0.12 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 107.2 (s), 84.3 (s), 67.4 (d), 63.5 (d), 33.4 (t), 28.6 (t), 27.1 (t), 25.4 (t), 25.2 (t), 19.6 (t), 18.6 (q), 0.0 (q); *m/z* (EI) 254 (MH^+, self CI, 10%), 172 (98), 165 (75), 110 (88), 100 (100), 97 (87), 96 (80), 84 (99), 41 (82); *m/z* (CI) 254 (MH^+, 100%), 238 (99), 236 (96); [Found: MH^+ 254.1940. $C_{14}H_{27}NOSi$ requires *MH* 254.1940].

The trans-*pyrrolidine* **26** was aslo isolated as a pale yellow oil (18 mg, 45%); R_f 0.09, 8:2 hexane-ethyl acetate; [Found: C, 66.6; H, 10.7; N, 5.5%. $C_{14}H_{27}NOSi$ requires C, 66.3; H, 10.7; N, 5.5%]; ν_{max} (thin film)/cm^{-1} 3239brm (O-H), 2174s (C≡C); δ_H (400 MHz, $CDCl_3$) 3.31-3.21 (1H, m, CH_3CHN), 3.20-3.07 (1H, m, CH_2CHN), 2.19 (2H, t, *J* 6.9, $CH_2C{\equiv}C$), 1.97-1.87 (2H, m), 1.57-1.33 (8H, m), 1.14 (3H, d, *J* 6.7, CH_3), 0.14 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 107.3 (s), 84.3 (s), 68.3 (d), 65.9 (d), 31.7 (t), 28.6 (t), 27.1 (t), 26.0 (t), 25.1 (t), 19.6 (t), 18.6 (q), 0.0 (q); *m/z* (EI) 254 (MH^+, 4%), 162 (54), 100 (97), 97 (80), 84 (100), 41 (68); *m/z* (CI) 254 (MH^+, 78%), 238 (100), 236 (65).

5-Methyl-2-(6'-trimethylsilyl-5'-hexynyl)-2,3-dihydro-(4H)-pyrrole-1-oxide **29**

1-Hydroxy-2-methyl-4-(6'-trimethylsilyl-5'-hexynyl)pyrrolidine (*cis* and *trans*) **25** and **26** (200 mg, 0.79 mmol) was dissolved in chloroform (10 cm^3) and stirred at room temperature for 2 weeks. The solvent was removed under reduced pressure, and the crude compound purified by flash column chromatography (silica, eluting 9:1 ethylacetate-methanol) to give product *nitrone* **29** (139 mg, 70%) and recovered starting material **25** and **26** (59mg). R_f 0.10, 9:1 Ethylacetate-methanol; ν_{max} (thin film)/cm^{-1} 2172s (C≡C), 1602m (C=N^+); δ_H (250 MHz, $CDCl_3$) 3.90-3.80 (1H, m, CHN^+), 2.55-2.45 (2H, t, *J* 9.8, CH_2-C≡C), 2.15-2.00 (4H, m), 1.90 (3H, s, CH_3-C=N), 1.65-1.40 (4H, m), 1.35-1.25 (2H, m, CH_2CHN^+), 0.05 (9H, s, $(CH_3)_3Si$); δ_C (100 MHz, $CDCl_3$) 143.3 (s), 107.0 (s), 84.8 (s), 72.2 (d), 31.9 (t), 28.3 (t), 24.1 (t), 22.8 (t), 19.7 (t), 12.8 (q), 0.1 (q); *m/z* (CI) 252 (MH^+, 100%), 236 (90); *m/z* (EI) 251 (M^+, 29%), 236 (41), 172 (33), 140 (100), 113 (55), 100 (66), 73 (93); [Found: MH^+ 252.1784 (CI). $C_{14}H_{25}NOSi$ requires *MH* 252.1784].

9-Trimethylsilyl-1-non-8-yn-5-one oxime **22**

Lithium diisopropylamide (1.5 mol dm^{-3} in hexane, 2.7 cm^3, 4 mmol) was added dropwise to a stirred solution of 5-hexen-2-one dimethylhydrazone **6** (560 mg, 4 mmol) in dry THF (10 cm^3) at 0 °C under nitrogen. The solution was stirred for 2 hours at 0 °C and 3-bromo-1-trimethylsilyl-1-propyne **17** (1 g, 4.6 mmol) was added dropwise at 0 °C under nitrogen. After 30 minutes the reaction was allowed to warm to 20 °C, and stirred for a further 12 hours. The reaction was quenched with water (4 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 4 cm^3), and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude *hydrazone* was isolated as a pale yellow oil. After removal of the solvent under reduced pressure, pyridine-ethanol (10 cm^3, 1:1) and hydroxylamine hydrochloride (1 g, 12 mmol) were added and the solution stirred at 20 °C for 2 hours. The solution was poured into aqueous

hydrochloric acid (2 M, 20 cm^3) and extracted with dichloromethane (4 x 20 cm^3). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 8:2 hexane-ether) to give pure *oxime* **22** (0.61 g, 71%) as a colourless oil; a mixture of *E* and *Z* oximes. R_f 0.55, 1:1 hexane-ether; [Found: C, 64.6; H, 9.5; N, 6.4%. $C_{12}H_{21}NOSi$ requires C, 64.5; H, 9.5; N, 6.3%]; ν_{max} (thin film)/cm^{-1} 3601m (OH), 3290 brs (OH), 3081m (*sp2*, CH), 2176s (C≡C), 1640m (C=C); δ_H (250 MHz, $CDCl_3$) 5.83-5.69 (1H, m, C*H*=CH_2), 5.10-5.07, 5.03-5.02 and 4.97-4.96 (2H, 3 x m, CH=CH_2), 2.53-2.26 (8H, m, CH_2), 0.13 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 159.6 (s), 137.4 (d), 137.2 (d), 115.3 (t), 115.2 (t), 106.0 (s), 105.9 (s), 85.3 (s), 34.2 (t), 33.3 (t), 29.9 (t), 29.5 (t), 28.0 (t), 27.2 (t), 17.1 (t), 16.2 (t), 0.0 (q); *m/z* (CI) 223 (MH^+, 100%), 208 (12), 90 (8); [Found: MH^+ 224.1471 (CI). $C_{12}H_{21}NOSi$ requires *MH* 224.1471].

(2R, 5S*)-1-Hydroxy-2-methyl-3-(4'-trimethylsilyl-3'-butynyl)pyrrolidine* **27** and *(2R*, 5R*)-1-Hydroxy-2-methyl-3-(4'-trimethylsilyl-3'-butynyl)pyrrolidine* **28**

A stirred solution of 9-trimethylsilyl-1-non-8-yn-5-one oxime **22** (500 mg, 2.23 mmol) in methanol (50 cm^3) was cooled to -10 °C under nitrogen. Sodium cyanoborohydride (280 mg , 4.14 mmol) and methyl orange indicator (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 minutes the solution was made strongly basic with 20% aqueous sodium hydroxide solution and poured into saturated brine (45 cm^3) containing ice. The suspension was extracted with dichloromethane (4 x 60 cm^3) and the organic extracts were combined and stirred over sodium sulphate for 1 hour at 20 °C. The solution was filtered, the solvent removed under reduced pressure and the crude products purified by flash column chromatography (silica, eluting 8:2 hexane-ethyl acetate) to give the cis-*pyrrolidine* **27** (102 mg, 20%) as a colourless oil. R_f 0.25, 1:1 pet. ether-ether; [Found: C, 64.2; H, 10.3; N, 6.3%. $C_{12}H_{23}NOSi$ requires C, 64.0; H, 10.3; N, 6.2%]; ν_{max} (thin film)/cm^{-1} 3354brs (O-H), 2174s (C≡C); δ_H (400 MHz, $CDCl_3$) 2.70-2.55 (2H, m, C*H*N), 2.20-2.10 (1H, m, CH_2CHCH_2), 2.21 (2H, t, *J* 7.0, $CH_2C{\equiv}C$), 1.69-1.62 (2H, m), 1.55-1.49 (2H, m), 1.30-1.20 (2H, m), 1.18 (3H, d, *J* 6.2, CH_3), 0.12 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$,) 107.5 (s), 84.3 (s), 67.1 (d), 63.4 (d), 32.7 (t), 27.2 (t), 25.1 (t), 18.5 (q), 16.9 (t), 0.0 (q); *m/z* (CI) 226 (MH^+, 100%), 210 (22); [Found: MH^+ 226.1627 (CI). $C_{12}H_{23}NOSi$ requires *MH* 226.1627].

The trans-*pyrrolidine* **28** (220 mg, 44%) was also isolated as a pale yellow oil. R_f 0.15, 1:1 pet. ether (60-80)-ether; [Found: C, 64.3; H, 10.3; N, 6.3%. $C_{12}H_{23}NOSi$ requires C, 64.0; H, 10.3; N, 6.2%]; ν_{max} (thin film)/cm^{-1} 3353brm (O-H), 2175s (C≡C); δ_H (200 MHz, $CDCl_3$) 3.31-3.09 (2H, m, C*H*N), 2.20 (2H, t, *J* 6.9, $CH_2C{\equiv}C$), 1.95-1.85 (2H, m), 1.57-1.33 (4H, m), 1.15 (3H, d, *J* 6.7, CH_3), 0.14 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 107.5 (s), 84.4 (s), 67.4 (d), 63.5 (d), 32.9 (t), 27.4 (t), 25.1 (t), 18.7 (q), 17.0 (t), 0.1 (q); *m/z* (CI) 226 (MH^+, 82%), 224 (51), 210 (50), 208 (49), 154 (100), 138 (41); [Found: MH^+ 226.1627 (CI). $C_{12}H_{23}NOSi$ requires *MH* 226.1627].

(3R, 6R*, 11S*)-11-methyl-2-oxa-1-azatricyclo[5.4.1^{3,11}.0]dodecane* **31** and *7-Methyl-2-(3-butenyl)-2, 3, 4, 5-tetrahydro-(6H)-azepine-1-oxide* **30**

(2R*, 5R*)-1-Hydroxy-2-methyl-4-(6'-trimethylsilyl-5'-butynyl)pyrrolidine (*trans*) **25** (100 mg, 0.4 mmol) was dissolved in dry toluene (30 cm^3), and the solution was thoroughly freeze-thaw degassed. The solution was heated in a sealed tube under argon, at 140 °C for 23 hours. On cooling the solvent was removed under reduced pressure and the crude product purified by flash column chromatography (silica, eluting 9:1 ethylacetate-methanol) to give *tricycle* **31** (43 mg, 60%) as a white solid. R_f 0.52, 9:1 ethylacetate-methanol;

m.p. 69-70 °C; [Found: C, 72.8; H, 10.7; N, 7.5%. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%]; ν_{max} (CCl_4)/cm^{-1} no peaks other than CH above 1500 cm^{-1}; δ_H (200MHz, $CDCl_3$) 4.48-4.43 (1H, m, C*H*O), 3.39 (1H, tt, *J* 8.9, 4.3, C*H*N), 2.26 (1H, dd, *J* 11.8, 7.6), 2.12-2.00 (2H, m), 1.96-1.13 (11H, m), 1.27 (3H, s, CH_3); δ_C (50MHz, $CDCl_3$) 76.8 (d), 68.6 (s), 63.6 (d), 50.5 (t), 38.9 (t), 32.8 (t), 31.6 (q), 30.4 (t), 26.3 (t), 24.1 (t), 22.0 (t); *m/z* (CI) 182 (100%); [Found: MH^+ 182.1545 (CI). $C_{11}H_{19}NO$ requires *MH* 182.1545] and *nitrone* **30** (11 mg, 15%). R_f 0.15, 9:1 Ethylacetate-methanol; ν_{max} (CCl_4)/cm^{-1}; δ_H (400MHz, $CDCl_3$) 5.85-5.75 (1H, m, C*H*=CH_2), 5.04-4.95 (2H, m, CH=CH_2), 4.15-4.04 (1H, m, C*H*-N^+), 2.61-2.57 (2H, m, $CH_2C=N^+$), 2.49-2.17 (4H, m), 2.16 (3H, br s, CH_3), 1.85 (6H, m); δ_C (100MHz, $CDCl_3$) 147.6 (s), 137.9 (d), 115.3 (t), 70.5 (d), 32.4 (t), 31.1 (t), 30.5 (t), 29.7 (t), 27.4 (t), 23.3 (t), 20.6 (q); *m/z* (CI) 198 (100%), 182 (MH^+, 65); [Found: MH^+ 182.1545 (CI). $C_{11}H_{19}NO$ requires *MH* 182.1545] and oxidised starting material as *nitrone* **29** (7 mg, 7%).

*(4*R*, *7*R*, *10*R*)--*10-methyl-2-oxa-1-azatricyclo[5.3.0.0^{4,10}]decane* **37**

trans-N-Hydroxypyrrolidine **28** (60 mg, 0.3 mmol) was dissolved in toluene (10 cm^3) and freeze-thaw degassed. The solution was heated to 140 °C in a sealed tube under argon for 20 hours. On cooling the solvent was removed under reduced pressure and the crude compound purified by flash column chromatography (silica, eluting 8:2 ether-hexane) to give pure tricycle **37** (24 mg, 52%) as a colourless oil. R_f 0.12, 8:2 hexane-ether; ν_{max} (thin film)/cm^{-1} no stretches other than C-H above 1500 cm^{-1}; [Found: C, 70.1; H, 9.9; N, 9.4%. $C_9H_{15}NO$ requires C, 70.5; H, 9.9; N, 9.2%]; δ_H (400MHz, $CDCl_3$) 4.10-4.05 (1H, m, C*H*O), 3.95 (1H, d, *J* 6.9, C*H*O), 3.51-3.43 (1H, m, C*H*N), 2.13-2.01 (5H, m), 1.88-1.77 (1H, m), 1.69-1.63 (1H, m), 1.52-1.42 (2H, m), 1.12 (3H, s, CH_3-); δ_C (100MHz, $CDCl_3$) 74.7 (t), 69.4 (s), 62.9 (d), 46.3 (d), 28.2 (t), 26.3 (t), 24.8 (t), 24.4 (q), 24.3 (t); *m/z* (EI) 153 (M^+, 42%), 99 (100), 82 (89), 55 (24); [Found: M^+ 153.1150 (EI). $C_9H_{15}NO$ requires *M* 153.1153].

12-Trimethylsilyl-2-dodec-11-yn-6-one oxime **39**

n-Butyllithium (1.5M in hexane, 14.9 cm^3, 22 mmol) was added dropwise to a stirred solution of diisopropylamine (2.9 cm^3, 22 mmol) in dry THF (25 cm^3) at 0 °C under nitrogen. After 10 minutes 5-hepten-2-one dimethylhydrazone (2.7 g, 17 mmol) was added dropwise at 0 °C under nitrogen. The solution was stirred for 2 hours at 0 °C, and 5-bromo-1-trimethylsilyl-1-pentyne **16** (3.3 g, 14.9 mmol) was added dropwise at -30 °C under nitrogen. The reaction was allowed to gradually warm to 20 °C, and stirred for a further 12 hours. The reaction was quenched with water (15 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (4 x 30 cm^3), and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude *hydrazone* was isolated as a pale yellow oil.

After removal of the solvent under reduced pressure, pyridine-ethanol (30 cm^3, 1:1) and hydroxylamine hydrochloride (3.2 g, 42.7 mmol) were added to the crude hydrazone and the solution stirred at 20 °C for 2 hours. The solution was poured into aqueous hydrochloric acid (2M, 200 cm^3) and extracted with dichloromethane (4 x 200 cm^3). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 7:3 hexane-ether) to give pure *oxime* **39** (2.6 g, 66%) as a colourless oil, a mixture of *E* and *Z* oximes. [Found: C, 68.0; H, 10.3; N, 5.2%. $C_{15}H_{27}NOSi$ requires C, 67.9; H, 10.3; N, 5.3%]; ν_{max} (thin film)/cm^{-1} 3250brs (O-H), 2174s (C≡C); δ_H (400MHz, $CDCl_3$) 8.75 (1H, br, s, NO*H*), 5.50-5.34 (2H, m, C*H*=C*H*), 2.40-2.37 (2H, m, CH_2C≡C), 2.16-2.16 (6H, m), 1.63-1.49 (4H, m), 1.61 (3H, dd, *J* 4.4 and 1.0, CH_3C=C), 0.12 (9H, s, $(CH_3)_3$Si); δ_C (100MHz, $CDCl_3$) 161.2 (s), 161.1 (s), 130.1 (d), 129.9 (d), 127.0

(d), 126.3 (d), 107.0 (s), 84.7 (s), 35.9 (t), 33.7 (t), 29.7 (t), 28.5 (t), 28.4 (t), 27.4 (t), 25.2 (t), 20.0 (t), 17.9 (q), 0.1 (q); *m/z* (CI) 266 (MH^+, 100%), 250 (85), 128 (18), 90 (12); [Found: MH^+ 266.1940 (CI). $C_{15}H_{27}NOSi$ requires *MH* 266.1940].

12-Trimethylsilyl-2-dodec-11-yn-6-one hydroxylamine **40**

Hydrochloric acid (6M in methanol) was added dropwise to a solution of the oxime **39** (1.08 g, 4.08 mmol), sodium cyanoborohydride (523 mg, 8.3 mmol) and methyl orange indicator (3 drops) in dry methanol (50 cm^3) at -10 °C under argon, so as to just keep the solution pink. After 35 minutes the solution was neutralised with aqueous ammonia, poured into brine containing ice (100 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic layers were dried (Na_2SO_4), the solvent removed under reduced pressure and the crude compound purified by flash column chromatography (silica, eluting 7:3 hexane-ether) to give *hydroxylamine* **40** (912 mg, 84%) as a pale yellow oil. R*f* 0.47, 1:1 hexane-ether; ν_{max} (CCl_4)/cm^{-1} 3607w (NH), 3311brm (OH), 2173s (C≡C); δ_H (400 MHz, $CDCl_3$) 5.85-5.50 (2H, m, C*H*=C*H*), 2.82-2.78 (1H, m, C*H*N), 2.23-2.19 (2H, m), 2.10-2.01 (2H, m), 1.62 (3H, d, *J*4.4, CH_3-), 1.58-1.46 (4H, m), 1.45-1.37 (4H, m), 0.12 (9H, s, (CH_3)$_3$Si-); δ_C ($CDCl_3$, 100 MHz) 130.9 (d), 125.3 (d), 107.3 (s), 84.5 (s), 61.1 (d), 31.1 (t), 30.9 (t), 28.9 (t), 28.5 (t), 24.9 (t), 19.7 (t), 17.9 (q), 0.14 (q); *m/z* (EI) 250 (M^+-OH, 22%), 238 (41), 186 (80), 178 (42), 152 (45), 114 (52), 73 (100), 55 (44); [Found: M-OH^+ 250.1991 (EI). $C_{15}H_{29}NOSi$ requires *M-OH* 250.1991].

(2R*, 5S*)*-1-Hydroxy-2-ethyl-4-(6'-trimethylsilyl-5'-hexynyl)pyrrolidine* **41**

A solution of hydroxylamine **40** (100 mg, 0.37 mmol) in dry degassed toluene (12 cm^3) was heated under reflux for 18 hours under argon. The solvent was removed under reduced pressure, and the product mixture purified by flash column chromatography (silica, eluting 75:25 hexane-ether) to give pure cis-*product* **41** (40 mg, 40%) as a colourless oil. R*f* 0.17, 7:3 hexane-ether; [Found: C, 67.7; H, 10.9; N, 5.2%. $C_{15}H_{29}NOSi$ requires C, 67.4; H, 10.9; N, 5.2%]; ν_{max} (CCl_4)/cm^{-1} 3356brm (O-H), 2174s (C≡C); δ_H (400 MHz, $CDCl_3$) 2.68-2.55 (2H, m, C*H*N), 2.20 (2H, t, *J* 7.0, CH_2C≡C), 1.89-1.83 (4H, m), 1.54-1.48 (2H, m), 1.40-1.22 (6H, m), 0.87 (3H, t, *J* 7.5, CH_3-), 0.12 (9H, s, (CH_3)$_3$Si-); δ_C (100 MHz, $CDCl_3$) 107.4 (s), 84.4 (s), 69.7 (d), 68.3 (d), 33.4 (t), 28.7 (t), 26.7 (t), 25.6 (t), 25.3 (t), 24.9 (t), 19.7 (t), 10.7 (q), 0.14 (q); *m/z* (EI) 267 (M^+, 10%), 250 (57), 238 (98), 186 (90), 114 (100), 73 (74); [Found: M^+ 267.2019 (EI). $C_{15}H_{29}NOSi$ requires *M* 267.2018].

6-Methyl-5-hepten-2-one dimethyl hydrazone **42**[37]

To a solution of 6-methyl-5-hepten-2-one (10 g, 71.4 mmol) in dry ethanol (50 cm^3) was added *N,N*-dimethyl hydrazone (16.1 cm^3, 210 mmol). The solution was gently refluxed for 3 hours. The solution was evaporated *in vacuo* to remove excess *N,N*-dimethyl hydrazone and ethanol. The residue was distilled under reduced pressure to give the hydrazone **42** (9.2 g, 78%) as a colourless liquid; ν_{max} (thin film)/cm^{-1} 3080m (C=CH), 1641s (C=N); δ_H (250 MHz, $CDCl_3$) a mixture of geometric isomers 5.10-5.00 (1H, m, C*H*=CMe_2), 2.35 (6H, 2 x s, NNMe_2), 2.15-2.10 (4H, m, -CH_2) 1.85 (3H, s, CH_3C=N), 1.62 (3H, s, (CH_3)$_2$C=C), 1.55 (3H, s, (CH_3)$_2$C=C); δ_C (63 MHz, $CDCl_3$) 167.5 (s), 132.0 (s), 123.2 (d), 49.6 (q), 38.8 (t), 31.3 (t), 24.9 (q), 16.5 (q), 15.1 (q).

1-Methyl-12-trimethylsilyl-2-dodec-11-yn-6-one oxime **44**

Lithium diisopropylamide (3.48 cm^3, 1.6M, 5.6 mmol) was added dropwise to a stirred solution of 6-methyl-5-hepten-2-one dimethylhydrazone **42** (1 g, 5.5 mmol) in dry THF (15 cm^3) at 0 °C under nitrogen. The solution was stirred for 2 hours at 0 °C, and 5-bromo-1-trimethylsilyl-1-pentyne **16** (1.43 g, 6.5 mmol) was added

dropwise at 0 °C under nitrogen. After 30 minutes the reaction was allowed to warm to 20 °C, and stirred for a further 12 hours. The reaction was quenched with water (10 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (4 x 20 cm^3), and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude *hydrazone* was isolated as a pale yellow oil. After removal of the solvent under reduced pressure, pyridine-ethanol (10 cm^3, 1:1) and hydroxylamine hydrochloride (0.3 g, 4 mmol) were added to the crude hydrazone (0.4 g, 1.3 mmol) and the solution stirred at 20 °C for 2 hours. The solution was poured into aqueous hydrochloric acid (2M, 10 cm^3) and extracted with dichloromethane (4 x 20 cm^3). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 7:3 pet. ether(60-80)-ether) to give pure *oxime* **44** (0.27 g, 74%) as a colourless oil, a mixture of *E* and *Z* oximes. [Found: C, 68.7; H, 10.6; N, 5.1%. $C_{16}H_{29}NOSi$ requires C, 68.8; H, 10.5; N, 5.0%]; ν_{max} (thin film)/ cm^{-1} 3243brs (O-H), 2860s (C=C), 2174s (C≡C); δ_H (400MHz, $CDCl_3$) 8.92 (1H, brs, N-O*H*), 5.13-5.07 (1H, m, C*H*=CMe_2), 2.37-2.32 (2H, m, CH_2-C≡C), 2.24-2.16 (6H, m), 1.65 (3H, s, CH_3-C=C), 1.59 (3H, 2 x s, CH_3-C≡C), 1.60-1.45 (4H, m), 0.12 (9H, s, $(CH_3)_3Si$); δ_C (100MHz, $CDCl_3$) 161.3 (s), 132.6 (s), 123.4 (d), 107.1 (s), 84.7 (s), 36.0 (t), 34.1 (t), 33.8 (t), 28.1 (t), 27.7 (t), 26.2 (q), 25.7 (t), 25.3 (t), 24.6 (t), 19.7 (t), 17.7 (q), 0.1 (q); *m/z* (CI) 280 (MH^+, 72%), 265 (23), 264 (100), 262 (24); [Found: MH^+ 280.2097 (CI). $C_{16}H_{29}NOSi$ requires *MH* 280.2097].

1-Methyl-12-trimethylsilyl-2-dodec-11-yn-6-one hydroxylamine **45**

Hydrochloric acid (6M in methanol) was added dropwise to a solution of the oxime **44** (300 mg, 1.08 mmol), sodium cyanoborohydride (105 mg, 1.7 mmol) and methyl orange indicator (2 drops) in dry methanol (20 cm^3) at -10 °C under argon, so as to just keep the solution pink. After 30 minutes the solution was neutralised with aqueous ammonia, poured into brine containing ice (20 cm^3) and extracted with dichloromethane (4 x 20 cm^3). The combined organic layers were dried ($MgSO_4$), the solvent removed under reduced pressure and the crude compound purified by flash column chromatography (silica, eluting ethylacetate to 9:1 ethylacetate-methanol) to give *hydroxylamine* **45** (240 mg, 80%) as a pale yellow oil. R_f 0.67, 9:1, ethylacetate-methanol; ν_{max} (thin film)/cm^{-1} 3683w (NH), 3590w (NH), 3200brm (OH), 2170s (C≡C, 1522s (C=C); δ_H (250 MHz, $CDCl_3$) 5.0-4.9 (1H, m, C*H*=C), 2.7-2.6 (1H, m, C*H*NHOH), 2.10 (2H, t, *J* 6.6, CH_2C=C), 1.55 (3H, s, CH_3-C=C), 1.45 (3H, s, CH_3-C=C), 1.45-1.20 (8H, m), 0.10 (9H, s, $(CH_3)_3Si$); δ_C (63 MHz, $CDCl_3$) 131.9 (s), 124.1 (d), 107.3 (s), 84.6 (s), 61.1 (d), 31.4 (t), 31.0 (t), 28.7 (t), 25.7 (q), 25.0 (t), 24.5 (t), 19.7 (t), 17.7 (q), 0.1 (q); *m/z* (CI) 282 (MH^+, 37%), 280 (100), 266 (49), 264 (56), 210 (15), 90 (19); [Found: MH^+ 282.2253 (CI). $C_{16}H_{31}NOSi$ requires *MH* 282.2253].

7-Methyl-2-(4'-methyl-pent-3'-enyl)-2,3,4,5-tetrahydro-(6H)-azepine-1-oxide **46**

A solution of the hydroxylamine **45** (160 mg, 0.64 mmol) in dry toluene (20 cm^3) was heated under reflux for 10 hours under argon. On cooling the solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 8:2 ethylacetate-methanol) to give *nitrone* **46** (110 mg, 82%) as a pale yellow oil. R_f 0.09, 9:1 ethylacetate-methanol; ν_{max} (thin film)/cm^{-1} 1584 (C=N^+), 1654 (C=C); δ_H (250 MHz, $CDCl_3$) 5.0-4.9 (1H, m, C*H*=C), 4.05-3.95 (1H, m, C*H*-N^+), 2.55-2.35 (2H, m, CH_2-C=N^+), 2.2-1.9 (2H, m), 1.70-1.40 (8H, m), 1.55 (3H, s, CH_3-C=C), 1.45 (3H, s, CH_3-C=C); δ_C (63 MHz, $CDCl_3$), 147.1 (s), 132.3 (s), 123.4 (d), 70.6 (d), 32.2 (t), 31.2 (t), 29.5 (t), 27.2 (t), 25.5 (q), 25.1 (t), 23.2 (t), 20.4 (q), 17.7 (q); *m/z* (EI) 210 (MH^+, 28%), 150 (40), 124 (38), 110 (100), 96 (50), 69 (49); *m/z* (CI) 210 (MH^+, 100%), 194 (46); [Found: M^+ 209.1775 (EI). $C_{13}H_{23}NO$ requires *M* 209.1779].

1-Methyl-10-trimethylsilyl-2-dec-9-yn-6-one oxime **43**

Lithium diisopropylamide (2.7 cm^3, 1.5M, 4 mmol) was added dropwise to a stirred solution of 6-methyl-5-hepten-2-one dimethylhydrazone **42** (4 g, 24 mmol) in dry THF (50 cm^3) at 0 °C under nitrogen. The solution was stirred for 2 hours at 0 °C, and 3-bromo-1-trimethylsilyl-1-propyne **17** (5.5 g, 25 mmol) was added dropwise at 0 °C under nitrogen. After 30 minutes the reaction was allowed to warm to 20 °C, and stirred for a further 12 hours. The reaction was quenched with water (100 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (4 x 100 cm^3), and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude *hydrazone* was isolated as a pale yellow oil. After removal of the solvent under reduced pressure, pyridine-ethanol (40 cm^3, 1:1) and hydroxylamine hydrochloride (4.2 g, 62 mmol) were added and the solution stirred at 20 °C for 2 hours. The solution was poured into aqueous hydrochloric acid (2M, 120 cm^3) and extracted with dichloromethane (4 x 120 cm^3). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting 7:3 pet. ether(60-80)-ether) to give pure *oxime* **43** (4.06 g, 64 %) as a colourless oil, a mixture of *E* and *Z* oximes. R*f* 0.45 and 0.40, 1:1 hexane-ether; [Found: C, 67.1; H, 10.1; N, 5.7%. $C_{14}H_{25}NOSi$ requires C, 66.9; H, 10.0; N, 5.6%]; ν_{max} (thin film)/cm^{-1} 3290brm (O-H), 2170 (C≡C); δ_H (250 MHz, $CDCl_3$) 8.70 (1H, br s, NO*H*), 5.12-5.06 (1H, m, CH_2CH=C), 2.60-2.15 (8H, m), 1.68 (1H, s, $(CH_3)_2$C=C), 1.58 and 1.62 (1H, s, $(CH_3)_2$C=C), 0.12 (9H, s, $(CH_3)_3$Si); δ_C (100 MHz, $CDCl_3$) 159.9. (s), 159.7 (s), 132.8 (s), 132.6 (s), 123.2 (d), 123.1 (d), 106.2 (s), 106.1 (d), 85.3 (s), 85.2 (s), 33.5 (t), 33.1 (t), 27.6 (t), 27.2 (t), 25.9 (q), 24.9 (t), 24.7 (t), 17.7 (q), 17.1 (t), 16.3 (t), 0.0 (q); *m/z* (CI) 252 (MH^+, 100%), 236 (83), 198 (31); [Found: MH^+ 252.1784 (CI). $C_{14}H_{25}NOSi$ requires *MH* 252.1784].

1-Methyl-10-trimethylsilyl-2-dec-9-yn-6-one hydroxylamine **47**

Hydrochloric acid (6M in methanol) was added dropwise to a solution of the oxime **43** (1 g, 3.6 mmol), sodium cyanoborohydride (500 mg, 7.5 mmol) and methyl orange indicator (2 drops) in dry methanol (100 cm^3) at -10 °C under argon, so as to just keep the solution pink. After 30 minutes the solution was neutralised with aqueous ammonia, poured into brine containing ice (100 cm^3) and extracted with dichloromethane (4 x 150 cm^3). The combined organic layers were dried ($MgSO_4$), the solvent removed under reduced pressure and the crude compound purified by flash column chromatography (silica, eluting pet. ether (60-80) to 1:1 pet. ether (60-80)-ether) to give *hydroxylamine* **47** (763 mg, 75%) as a pale yellow oil. R*f* 0.65, 9:1, ethylacetate-methanol; ν_{max} (thin film)/cm^{-1} 3261brm (O-H), 2173s (C≡C); δ_H (250 MHz, $CDCl_3$) 5.0-4.9 (1H, t, *J* 6.6, CH=CH_2), 2.8-2.7 (1H, m, C*H*-NHOH), 2.25-2.1 (2H, t, *J* 7.3, CH_2C≡C), 1.95-1.85 (2H, dt, *J* 6.6 and 6.7, CH_2CH=C), 1.60-1.30 (4H, m, CH_2), 1.55 (3H, s, CH_3-C=C), 1.45 (3H, s, CH_3-C=C), 0.10 (9H, s, $(CH_3)_3$-Si); δ_C (63 MHz, $CDCl_3$) 131.9 (s), 123.8 (d), 107.2 (s), 84.8 (s), 60.3 (d), 31.3 (t), 30.2 (t), 25.6 (q), 24,0 (t), 17.6 (q), 16.6 (t), 0.0 (q); *m/z* (CI) 254 (MH^+, 8%), 238 (24), 184 (22), 182 (100), 166 (38); [Found: MH^+ 254.1940(CI). $C_{14}H_{27}NOSi$ requires *MH* 254.1940].

2-(4'-Methyl-3'-pentenyl)-5-methyl-2,3-dihydro-(4H)-pyrrole-1-oxide **48**

A solution of the hydroxylamine **47** (50 mg, 0.2 mmol) in dry toluene (10 cm^3) was heated under reflux for 24 hours under argon. On cooling the solvent was removed under reduced pressure and the compound purified by flash column chromatography (silica, eluting ethylacetate to 9:1 ethylacetate-methanol) to give *nitrone* **48** (20 mg, 56%) as a pale yellow oil. R*f* 0.11, 9:1 ethylacetate-methanol; δ_H (250 MHz, $CDCl_3$) 5.0-4.9 (1H, m, C*H*=C), 4.35-4.25 (1H, m, C*H*-N^+), 2.55-2.45 (2H, t, *J* 10, CH_2-C=N^+), 2.20-2.0 (2H, m), 1.85 (3H, s,

CH_3-C=N$^+$), 1.70-1.45 (4H, m), 1.55 (3H, s, CH_3-C=C), 1.45 (3H, s, CH_3-C=C); δ_C (63 MHz, $CDCl_3$), 143.1 (s), 132.4 (s), 123.0 (d), 71.8 (d), 60.3 (t), 32.4 (t), 31.0 (t), 25.6 (q), 23.7 (t), 22.9 (t), 17.6 (q), 12.7 (q); *m/z* (EI) 182 (MH^+, 93%, self CI), 123 (48), 99 (71), 83 (60), 55 (52), 41 (70); *m/z* (CI) 363 (dimer+H), 182 (MH^+, 100%), 166 (63); [Found: M^+ 181.1468 (EI). $C_{11}H_{19}NO$ requires *M* 181.1468].

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