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X=Y–ZH Systems as Potential 1,3-Dipoles. Part 50:[1] Phenylselenyl Halide Induced Formation of Cyclic Nitrones from Alkenyl Oximes

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Abstract—Oximes possessing γ-, δ or ω-alkenyl substituents are cyclised by phenylselenyl bromide, or by phenylselenyl chloride and an appropriate silver salt to the corresponding cyclic nitrones; the seleno nitrones undergo facially specific cycloaddition reactions with *N*-methylmaleimide; bis(alk-γ,δ-enyl) ketones undergo regiospecific cyclisation and stereospecific intramolecular cycloaddition to furnish spirocyclic products.

Inter- and intra-molecular cycloaddition reactions of nitrones have attracted much attention because they provide a potentially flexible entry into the complex molecular framework of natural products.[2] Utilising oximes as nitrone precursors in tandem nitrone generation-cycloaddition protocols substantially enhances this flexibility. We have recently introduced a range of such protocols[3] most of which have four distinct synthetic variants depending on whether the nitrone forming step or the cycloaddition step is inter- or intra-molecular (Table 1).

Electrophile induced cyclisation reactions are a well established strategy for the formation of hetero- and carbo-cyclic systems.[4] We have been exploring the generality of electrophile induced oxime-olefin (alkyne) reactions as a source of novel cascade nitrone formation-cycloaddition protocols (Scheme 1).[5]

Oximes are potentially ambident nucleophiles with either N or O acting as the reactive site depending on the co-reagents, solvent and pH of the reaction mixture. Nucleophilic nitrogen leads to the desired reaction (Scheme 1) whilst nucleophilic oxygen leads to oxime ethers (intermolecular process) or oxazines (intramolecular process) (Scheme 2). Oximes are attractive precursors of nitrones because of their ease of preparation, their impressive diversity and range of molecular complexity coupled with the corresponding features present in the nitrone cycloaddition products, the isoxazolidines, and the latter's potential for further synthetic manipulation.

In this paper we report more fully on our studies concerned with phenylselenyl halide.[6] In a preliminary evaluation of phenylselenyl halides[7] it became clear that phenylselenyl bromide in combination with silver triflate, usually gave rise to cleaner reactions and improved yields compared with phenylselenyl chloride alone or phenylselenyl chloride in combination with silver tetrafluoroborate. We now report full details of our studies of these processes. Subsequent to our preliminary communication Tiecco et al. have published similar observations using persulphate in combination with diphenyl diselenide to generate the electrophilic phenylselenyl species.[8]

Oxime **1a** (*E*/*Z* 2:1) reacted (CH_2Cl_2, 25°C, 0.5 h) with phenylselenyl bromide (1.0 mol) to give the cyclic nitrone salt **2a**. Treatment with anhydrous potassium carbonate (1.1 mol) (CH_2Cl_2, 25°C, 16 h) afforded the corresponding nitrone **6a** together with a trace of oxazine **3a**. Heating the nitrone **6a** in acetonitrile (80°C, 9 h) with *N*-methylmaleimide (NMM) (1 mol) afforded a 3:2 mixture (70% overall

Table 1. Synthetic variants of oxime→nitrone→cycloaddition cascades

Class	Nitrone formation	Cycloaddition
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular

Keywords: cyclic nitrones; alkenyl oximes; cycloaddition cascades.
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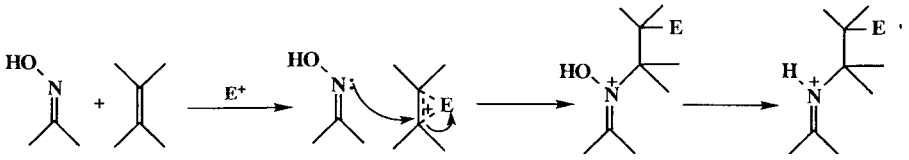
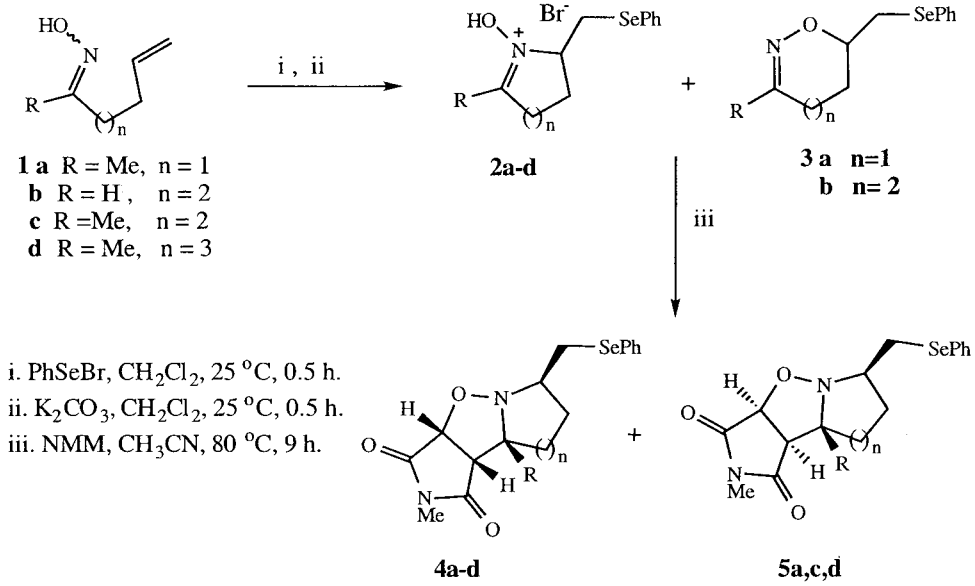
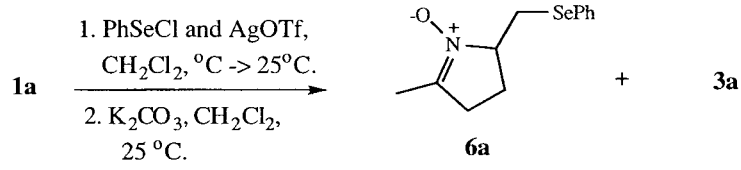


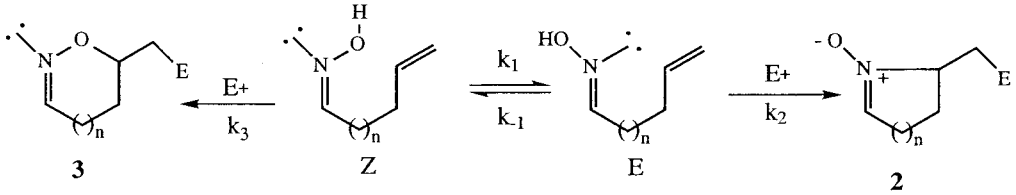
Scheme 1.

from **1a**) of *endo*- and *exo*-cycloadducts **4a** and **5a**, respectively. The diastereofacially specific cycloaddition of this and all the nitrones in this paper accords with our observations on related cases.[3,5] The stereochemistry of **4a** and **5a** were assigned from nOe data (see Experimental). It is apparent from this result that the ratio of nitrone **2a** to oxazine **3a** does not reflect the *E*:*Z* ratio of the oxime. The nitrone:oxazine ratio is sensitive to the reagents and conditions as shown by reaction of **1a** with PhSeCl–AgOTf (CH_2Cl_2, 0°C) to give **6a** followed by treatment with potassium carbonate (CH_2Cl_2, 25°C, 16 h) which affords a 2.5:1 mixture of **6a** and **3a** in 76% combined yield. The relationship between the *E*/*Z*-oxime ratio and the formation of **2** or **3** is summarised in Scheme 2.

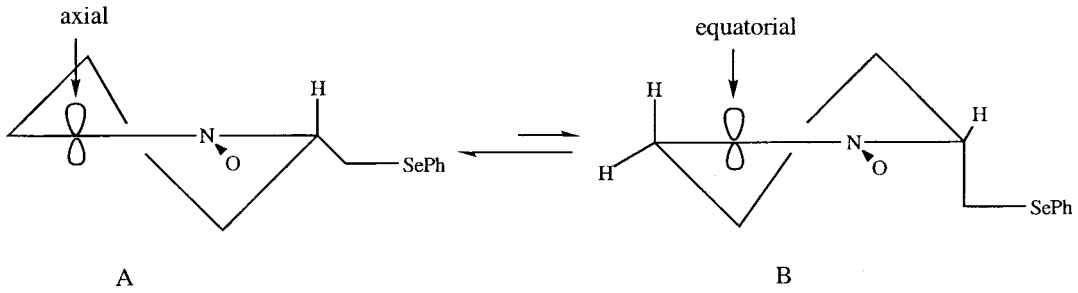
The outcome of the electrophile induced cyclisation depends on the relative values of k_1, k_{-1}, k_2 and k_3 (Scheme 2). The cyclisation would be expected to be the rate limiting steps for the more stable *E*-isomer whilst for the *Z*-isomer k_1 or k_3 may be rate limiting depending on factors that control







Scheme 2.



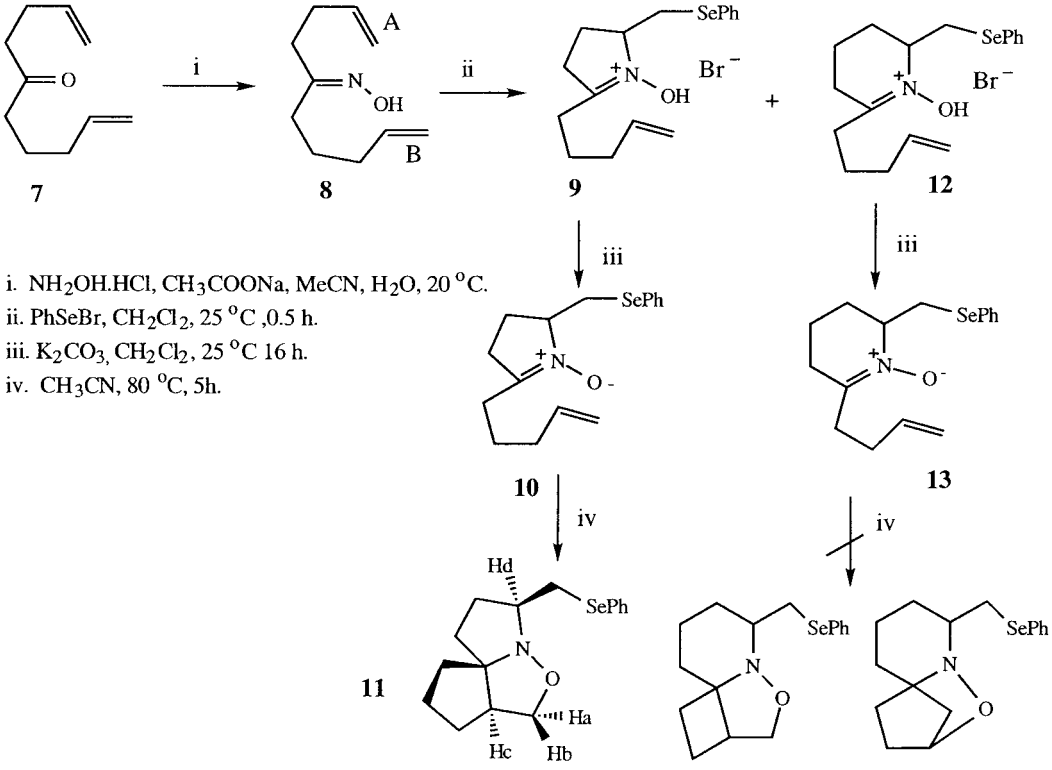
Scheme 3.

the relative rates of k_1 versus k_3. Clearly under the conditions applied to the formation of **6a** (above) $k_{-1}>k_3$.

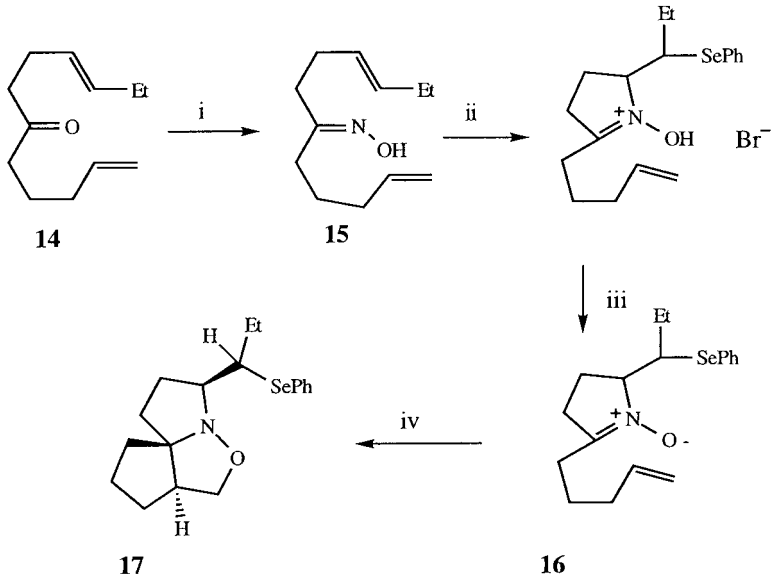
Oxime **1b** (*E*/*Z* 1:1) reacted under analogous conditions to give the corresponding nitrone salt **2b**. Neutralisation and 1,3-dipolar cycloaddition afforded a single *endo*- cycloadduct **4b** (61% overall from **1b**). In this case none of the corresponding oxazine was observed. The stereochemistry of **4b** was assigned from nOe data (see Experimental). The oxime **1c** reacted under the same conditions to give a 3:2 mixture (72%) of *endo*- and *exo*-cycloadducts **4c** and **5c**, respectively, but again no oxazine was detected. The stereochemistry of **4c** and **5c** was assigned from nOe data (see Experimental). These studies were then extended to the generation of 7-membered cyclic nitrone **2d**. 7-Octen-2-one oxime **1d** reacted with PhSeBr (CH_3CN, 48 h, 25°C) to give nitrone salt **2d** [the reaction could also be carried out by heating in acetonitrile (50°C, 4 h)] which upon treatment with anhydrous K_2CO_3 and NMM (CH_3CN, 25°C, 16 h) gave a 3:1 mixture (55%) of *endo*-**4d** and *exo*-**5d** cycloadducts. Stereochemical assignments were again based on nOe data (see Experimental). The conversions of oximes **1a–d** into cycloadducts **4a–d** and **5a,c,d** constitute examples of Class 3 processes (Table 1).

The cycloadditions occur *trans* to the CH_2SePh substituent for the cyclic nitrones **2a–d**. This outcome points to stereoelectronic effects in the cycloaddition transition state as illustrated in Scheme 3 for the 6-membered nitrone.

In the more stable conformer A (partial MO only is shown for clarity) attack on the face of nitrone anti to the equatorial CH_2SePh group involves axial C–C bond formation in the transition state whilst in the less stable conformer B (partial MO only is shown for clarity) attack anti to the axial CH_2SePh involves equatorial C–C bond formation as the cycloaddition transition state develops towards product. Similarly attack *syn* to the CH_2SePh substituent in A



Scheme 4.

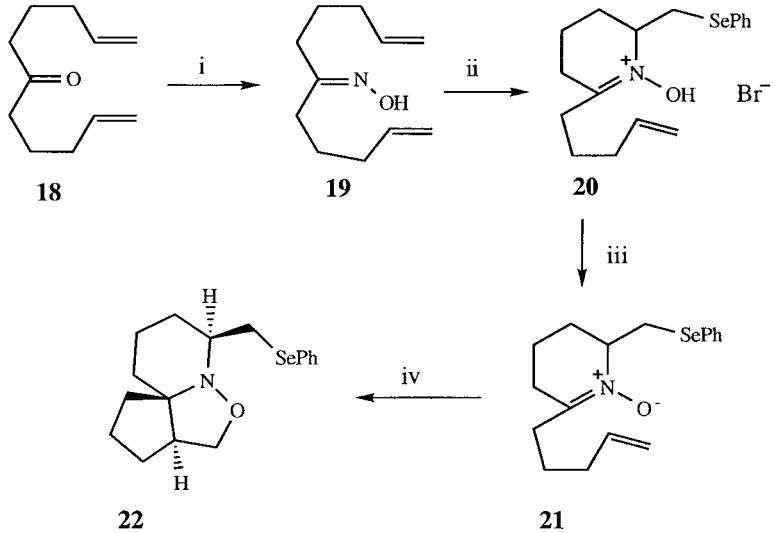


Scheme 5.

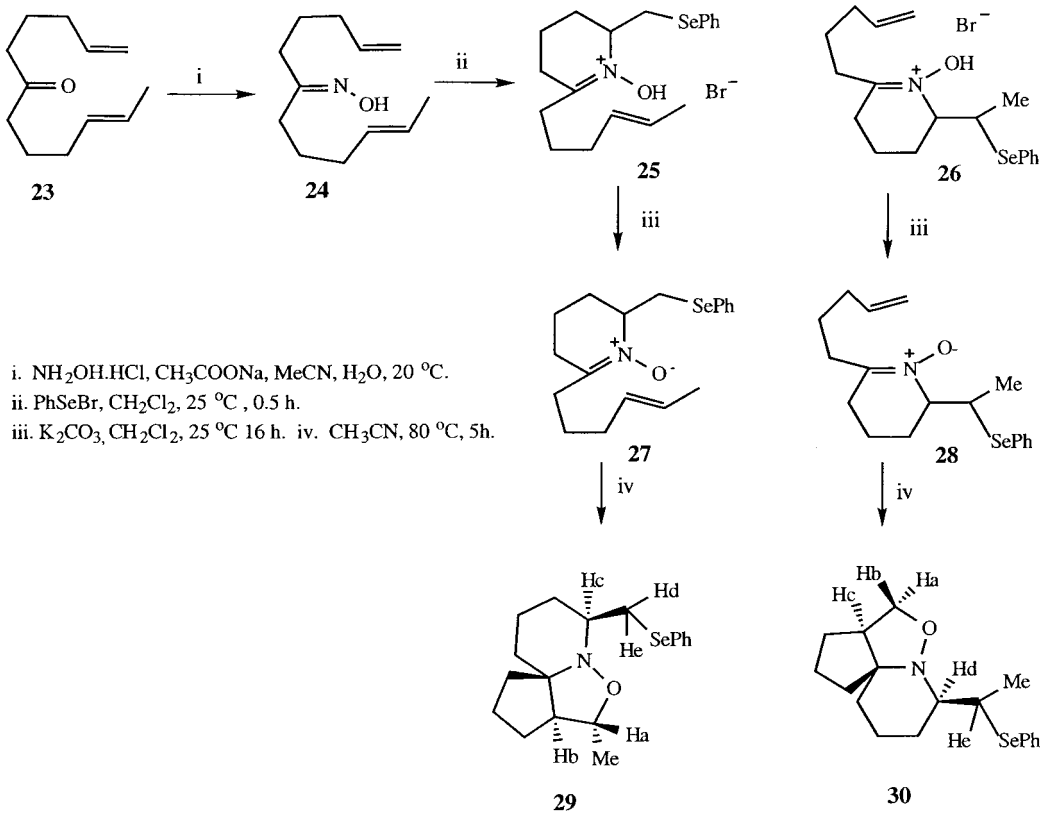
involves equatorial C–C bond formation whilst *syn* attack on B is destabilised by developing axial–axial interactions between the forming C–C bond and the CH_2SePh moiety.

Class 4 processes (intramolecular nitrone formation–intramolecular cycloaddition) have been explored with both symmetrical and unsymmetrical ketoximes. We first instigated a study into the effect of ring size (5-versus 6-membered) as a controlling factor in defining the regioselectivity of nitrone formation. Dialkenyl oxime **8**, in which both the alkene moieties are terminal was investigated first. Electrophilic attack at bond A would lead, via salt **9**, to the 5-membered ring nitrone **10** via a 5-*exo-tet* attack on the intermediate selenonium ion whilst electrophilic attack at bond B would lead, via a 6-*exo-tet* process, to 6-membered nitrone salt **12**. Treating **8** with PhSeBr and then K_2CO_3 afforded a 5:2 mixture of **10** and **13**. Heating this mixture (CH_3CN, 90°C, 5 h), afforded only **11** (35% overall from **8**) whilst nitrone **13** did not undergo cycloaddition. The failed intramolecular cycloaddition of **13** reflects the higher transition state energies involved in forming a strained subsiduary 4-membered ring or a [2.2.1]-bridged ring (Scheme 4).

The stereochemistry of **11** was assigned on the basis of nOe difference spectroscopy. Irradiation of the signal for Hc (δ 2.97) resulted in a 5.2% enhancement of the signal for Hd (δ 3.28), thus defining the *cis*-relationship between Hc and Hd and the stereochemistry at the spiro centre, and 4.9% enhancement of the signal at (δ 4.05) which is therefore assigned to Ha. The CH_aH_bO moiety gives rise to two signals, one at δ 4.05 (Ha) and the other at δ 3.61(Hb).



Scheme 6. (i) $NH_2OH{\cdot}HCl$, CH_3COONa, MeCN, H_2O, 20°C. (ii) PhSeBr, CH_2Cl_2, 25°C, 0.5 . (iii) K_2CO_3, CH_2Cl_2, 25°C, 16 h. (iv) CH_3CN, 80°C, 5 h.

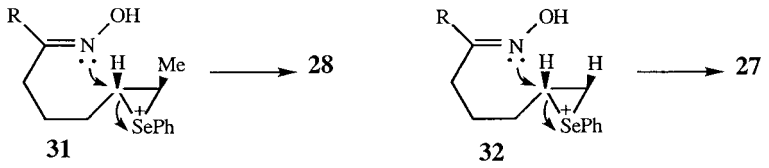


Scheme 7.

A similar sequence of reactions was performed on the unsymmetrical ketoxime **15**. Regiospecific cyclisation (CH_3CN, 25°C) to nitrone **16** occurred on treatment of **15** sequentially with phenylselenyl bromide and potassium carbonate. Heating **16** in acetonitrile (80°C, 4 h) afforded a single cycloadduct **17** (61% from **15**) via the anticipated diastereofacially specific cycloaddition (Scheme 5). The stereochemistry of the cycloadduct **17** was established by ^1H NMR decoupling experiments and nOe studies (see Experimental).

The formation of both nitrone salts **9** and **12** from oxime **8** indicates comparable rates of cyclisation via the corresponding 5- and 6- membered transition states with non-selective selenonium ion formation at bonds A and B. The addition of the terminal ethyl substituent in **15** creates a more electron rich environment at the Δ^9-alkene and promotes regioselective selenonium ion formation. Studies were next extended to the symmetrical diketone **18**. Oxime **19** reacted (CH_3CN, 25°C, 16 h) with phenylselenyl bromide to afford nitrone salt **20**. Treatment of **20** with anhydrous potassium carbonate afforded nitrone **21** which on heating in boiling acetonitrile afforded a single spirocyclic cycloadduct **22** (65% overall from **19**) (Scheme 6). The stereochemistry of the cycloadduct **22** was established by decoupling experiments and nOe studies (see Experimental).

The unsymmetrical diketone **23** was prepared to study the selectivity of electrophile mediated cascades of its oxime **24**. Cyclisation of **24** in the presence of PhSeBr (CH_3CN, 25°C 2h) and anhydrous K_2CO_3 (CH_3CN, 25°C, 2 h), added sequentially, gave a 2:1 mixture of nitrones **27** and **28**, respectively, via the nitrone salts **25** and **26**. The nitrones were not isolated but were trapped in an intramolecular cycloaddition by heating the mixture of nitrones in acetonitrile (80°C, 4 h) to afford the corresponding cycloadducts **29** (47%) and **30** (25%) (isolated overall yield from **24**). The stereochemical assignment of **29** is based on nOe data. Irradiation of the signal for Hb (δ 2.14) resulted in a 7% enhancement of the signal for Hc(δ 2.88) and a 4% enhancement of the signal for Me (δ 1.20). The signal for Ha (δ, 3.69) showed zero enhancement. The result established a *cis*-relationship between Hc, Hb and Me



Scheme 8.

together with the relative stereochemistry of the spiro centre which is the outcome of the expected concerted diastereofacially specific cycloaddition of the *E*-alkene to the nitrone **27** (Scheme 7). The stereochemistry of **30** was also assigned from nOe data (see Experimental).

It is clear from the results with oxime **24** that there is both a much reduced and reversed regioselectivity of nitrone formation in this case compared to the corresponding result with oxime **15**. Thus the expected selectivity for selenonium ion formation at the more substituted double bond of **24** is not observed. A possible explanation of these results is that the transition state for the 6-*exo-tet* cyclisation of the oxime moiety onto the selenonium ion **31→28** involves a developing destabilising $A^{1,2}$-strain[9] between the N–O bond and the MeCHSePh moiety requiring a higher activation energy for this process compared to that for cyclisation of the oxime moiety onto selenonium ion **32→27** (Scheme 8).

Experimental

Nuclear magnetic resonance spectra and decoupling experiments were determined at 300 MHz on a QE 300 instrument and at 400 MHz on a Bruker AM400 spectrometer. Data refer to 300 MHz unless otherwise specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad and brs=broad singlet. Infra-red spectra were recorded on a PU9706 IR Spectrophometer. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Kieselgel columns were packed with silica gel GF_{254} (Merck 7730). Petroleum ether refers the fraction with bp 40–60°C unless otherwise specified. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo–Erba Model 1106 instrument. Mass spectra were recorded at 70 ev on a VG Autospec mass spectrometer. Oximes (**1a–d**),[10] **8**,[11] **15**[12] and **24**[12] were prepared by literature methods.

General procedure for the oximation of aldehydes and ketones

$NH_2OH{\cdot}HCl$ (1.20 mmol) and NaOAC (1.50 mmol) were added to a stirred solution of the aldehyde or ketone (1.00 mmol) in 3:1 v/v $CH_3CN–H_2O$ (30 mL) at room temperature and stirring continued for a further 3 h. Most of the CH_3CN was removed under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with water (30 mL), dried ($MgSO_4$), filtered, the solvent removed under reduced pressure and the residue subjected to column chromatography on silica, eluting with petroleum ether–diethyl ether.

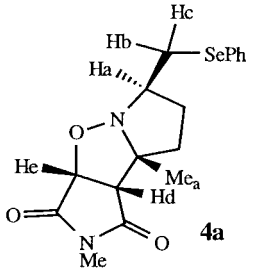
1, 10-Undecadien-6-one oxime 19. Obtained (76%) as a colourless oil. (Found: C, 73.0; H, 10.8; N, 7.8. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.55; N, 7.75%.); *m/z* (%) 181 (M^+, 1), 164 (10), 140 (13), 127 (77), 112 941), 73 (97), 55, (47) and 41 (100). δ: 1.61 (m, 4H, 2×CH_2), 2.09 (m, 4H, CH_2), 2.35 and 2.20 (2×m, 2×2H, 2×CH_2), 5.00 (m, 4H, CH=CH_2), 5.84 (m, 2H, CH=CH_2) and 8.8 (brs, 1H, OH).

endo-2,8a-Dimethyl-6-phenylselenylmethyl-hexahydro-dipyrrolo[1,2-*b*;3′,4′-*d*]isoxazole-1,3-dione (4a) and *exo*-2,8a-dimethyl-6-phenylselenylmethyl-hexahydro-dipyrrolo[1,2-*b*;3′,4′-*d*]isoxazole-1,3-dione (5a)

PhSeBr (0.21 g, 0.88 mmol) was added to a stirred solution of oxime **1a** (0.1 g, 0.88 mmol) in dry dichloromethane (10 mL) and the mixture was stirred at rt for 0.5 h, during which time quantitative conversion of the oxime into the corresponding nitrone salt **2a** occurred. Anhydrous K_2CO_3 (0.12 g, 0.88 mmol) was added and the reaction mixture was stirred overnight to liberate the nitrone (proton NMR showed a trace amount of the oxazine **3a**). The dichloromethane was removed under reduced pressure, the residue taken up in dry CH_3CN (10 mL), NMM (0.1 g, 0.88 mmol) added and the mixture heated at 80°C for 9 h. After cooling the solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with 1:1 v/v petroleum ether–diethyl ether to give to give the *product* (0.23 g, 70% overall from oxime) as a 3:2 mixture of *endo*- and *exo*- isomers. The isomers were separated by fractional crystallisation from ethyl acetate–ether.

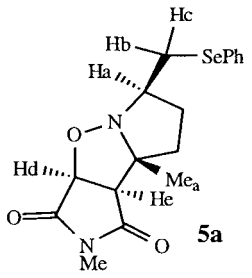
4a. Obtained as colourless rods, mp 138.5–139.5°C. (Found: C, 53.5; H, 5.34; N, 7.1. $C_{17}H_{20}N_2O_3Se$ requires C, 53.8; H, 5.27; N, 7.38%). *m/z* (%) 379 (M^+, 34), 209 (100), 98 (28) and 55 (56). δ (400 MHz): 7.4 (m, 2H, ArH), 7.2 (m, 3H, ArH), 4.9 (d, 1H, *J*=7.8 Hz, Hd), 3.3 (m, 2H, Hb and He), 2.9 (m, 1H, Ha), 2.8 (dd, 1H, *J*=12.2 and 8.8 Hz, Hc), 2.7 (s, 3H, NMe), 2.56 (m, 1H), 1.96 (m, 1H), 1.8 (m, 1H), 1.61 (m, 1H) and 1.4 (s, 3H, Me).

NOEDS (%) (400 MHz) irradiation of the proton signal for Hd caused enhancements of the proton signal for He (9.5). Irradiation of the proton signal for Me_a caused an enhancement of proton signal for He (4.7).



4a

5a. Obtained as colourless rods, mp 128–129°C. (Found: C, 53.65; H, 5.2; N, 7.45. $C_{17}H_{20}N_2O_3Se$ requires C, 53.8; H, 5.27; N, 7.38%). *m/z* (%) 380 (M^+, 8), 209 (100), 95 (45) and 55 (28). δ (400 MHz): 7.5 (m, 2H, ArH), 7.3 (m, 3H, ArH), 4.86 (d, 1H, *J*=7.8 Hz, Hd), 3.5 (m, 1H, Ha), 3.4 (d, 1H, *J*=7.8 Hz, He), 3.3 (dd, 1H, *J*=12.1 and 5.0 Hz, Hb), 3.0 (s, 3H, NMe), 2.8 (dd, 1H, *J*=12.1 and 9.8 Hz, Hc), 2.3 (m, 1H), 2.1 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H) and 1.2 (s, 3H, Me).

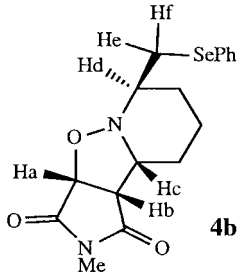


5a

Enhancement (%)

Irradiated hydrogen	Ha	Hc	Hd	He
Ha			8.6	
Hd	2.5			7.7
Me$_a$		1.5		

***endo*-2-Methyl-7-phenylselenylmethyl-hexahydro-8-oxa-2,7a-diaza-cyclopenta[*a*]indene-1,3-dione (4b).** A solution of 5-hexanal oxime **1b** (0.10 g, 0.88 mmol) and PhSeBr (0.21 g, 0.88 mmol) in dry CH_3CN (10 mL) was stirred at room temperature for 0.5 h. Anhydrous K_2CO_3 (0.12 g, 0.88 mmol) and NMM (0.20 g, 1.77 mmol) were then added sequentially and the reaction mixture heated at 80°C for 5 h. After cooling the solvent was removed under reduced pressure and the residue purified by Kieselgel column chromatography, eluting with 1:1 v/v diethyl ether–petroleum ether afforded the *product* (0.23 g, 61%) as a single stereoisomer which crystallised from ethyl acetate–petroleum ether as colourless fine needles, mp 104–105°C. [Found (HRMS) 380.0632, $C_{17}H_{21}N_2O_3Se$ requires 380.0639]. *m/z* (%) 380(M+1, 3), 253 (4), 209 (100), 158 (19), 111 (7), 82(23) and 41 (35). ν_{max} (nujol): 1780, 1710, 1580, 1420, 1310, 1290, 1130, 1070, 960, 730, 690, 630 and 610 cm^{-1}: δ: 7.52 (m, 2H, ArH), 7.26 (m, 3H, ArH), 4.71 (d, 1H, *J*=7.7 Hz, Ha), 3.6 (m, 1H, Hd), 3.40 (m, 2H, Hb and CHSe), 3.00 (s, 3H, NMe), 2.79 (m, 2H, Hc and CHSe), 2.09 (m, 3H), 1.63 (m, 1H) and1.38 (m, 2H).



4b

Enhancement (%)

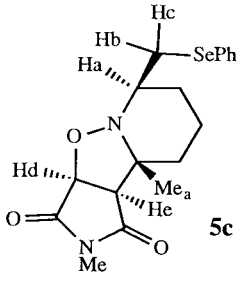
Irradiated hydrogen	Ha	Hb+He	Hc+Hf
Ha		6.2	3.9
Hb+He	7.1		6.7
Hc	5.7	20.9	

***endo*-2,3b-Dimethyl-7-phenylselanylmethyl-hexahydro-8-oxa-2,7a-diaza-cyclopenta[a]indene-1,3-dione (4c) and *exo*-2,3b-dimethyl-7-phenylselanylmethyl-hexahydro-8-oxa-2,7a-diaza cyclopenta[*a*]indene-1,3-dione (5c)**

PhSeBr (0.18 g, 0.78 mmol) was added to a stirred solution of oxime **1c** (0.1 g, 0.78 mmol) in dry dichloromethane (10 mL) and the mixture was stirred at rt for 0.5 h during which time quantitative conversion of oxime into the corresponding nitrone salt **2c** occurred. Anhydrous K_2CO_3 (0.108 g, 0.78 mmol) was added and the reaction mixture was stirred overnight to liberate the nitrone. The mixture was filtered and to remove inorganic salts, dichloromethane was removed under reduced pressure and the residue was taken up in dry CH_3CN (10 mL), NMM (0.1 g, 0.88 mmol) added and the mixture heated at 80°C for 9 h. After cooling the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 1:1 v/v petroleum ether–diethyl ether to give to give the *product* (0.22 g, 72% overall yield) as a 3:2 mixture of *endo*- and *exo*-isomers. The isomers were separated by fractional crystallisation from ethyl acetate–petroleum ether.

4c. Obtained as colourless rods, mp 111.5–112.5°C. (Found: C, 54.85; H, 5.55; N, 7.1. $C_{18}H_{22}N_2O_3Se$ requires C, 54.9; H, 5.6; N, 7.1%). *m/z* (%) 393 (M^+, 20), 223 (100), 91 (45) and 41 (67). δ. 7.45 (m, 2H, ArH), 7.25 (m, 3H, ArH), 4.8 (d, 1H, *J*=7.98 Hz, Hd), 3.4 (dd, 1H, *J*=12.3 and 2.9 Hz, Hb), 3.24 (d, 1H, *J*=7.98 Hz, He), 2.89 (dd, 1H, *J*= 12.3 and 8.75 Hz, Hc), 2.78 (s, 3H, NMe), 2.62 (m, 1H, Ha), 2.42 (m, 1H), 1.97 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 1.34 (s, 3H, Me) and 1.14 (m, 2H).

5c. Obtained as colourless needles, mp 131.5–132.5°C. (Found: C, 54.95; H, 5.65; N, 7.15. $C_{18}H_{22}N_2O_3Se$ requires C, 54.9; H, 5.6; N, 7.1%). *m/z* (%) 393 (M^+, 56), 223 (93), 98 (20) and 41 (43). δ (400 MHz) (C_6D_6): 7.46 (m, 2H, ArH), 7.0 (m, 3H, ArH), 4.26 (d, 1H, *J*= 8.36 Hz, Hd), 3.55(dd, 1H, *J*=12.6 and 8.9 Hz, Hb), 2.7 (d, 1H, *J*= 8.3 Hz, He), 2.66 (dd, 1H, *J*=12.6 and 8.9 Hz, Hc), 2.54 (s, 3H, NMe), 2.35 (m, 1H, Ha), 1.86 (m, 2H), 1.26 (m, 1H), 1.1 (s, 3H, Me), 1.08 (m, 1H) and 0.9 (m, 2H).



5c

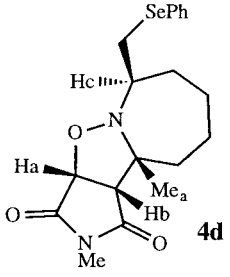
Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me$_a$
Ha		12.7	7.6	
Hb	7.8			
Me$_a$			1.5	

***endo*-2,3b-Dimethyl-8-phenylselenylmethyl-octahydro-9-oxa-2,8a-diaza-cyclopenta[*a*]azulene-1,3 dione (4d) and *exo*-2,3b-dimethyl-8-phenylselanylmethyl-octahydro-9-oxa-2,8a-diaza-cyclopenta[*a*]azulene-1,3-dione (5d)**

A solution of 7-octen-2-one oxime **1d** (0.30 g, 2.12 mmol) and PhSeBr (0.5 g, 2.12 mmol) in dry CH_3CN (15 mL) was stirred at room temperature for 48 h. Triethylamine (0.23 g, 0.31 mmol) and NMM (0.24 g, 2.12 mmol) were then added sequentially and the reaction mixture heated at 80°C for 16 h. After cooling the solvent was removed under reduced pressure and the residue purified by Kieselgel column chromatography, eluting with 1:1 v/v diethyl ether–hexane to afford the *product* (0.45 g, 55%) as a 3:1 mixture of *endo*-**4d** and *exo*-**5d**.

4d. Obtained as colourless fine needles from ethyl acetate–hexane, mp 101–102°C. (found: C, 56.2; H, 6.1; N, 6.8. $C_{19}H_{24}N_2O_3Se$ requires C, 55.9; H, 5.9; N, 6.9%). *m/z* (%) 408(M+1, <1), 237(100), 140(74), 111 (21), 77(20) and 41 (47). ν_{max} (nujol): 2990, 1850, 1680, 1420, 1340, 1260, 1120, 1000, 960, 840, 720 and 670 cm^{-1}. δ (400 MHz) (C_6D_6): 7.57(m, 2H, ArH), 6.94 and 6.99 (2×m, 3H, ArH), 4.05 (d, 1H, *J*=7.7 Hz, Ha), 3.43 (dd, 1H, *J*=2.1 and 11.2 Hz, CHSe), 3.15 (dd, 1H, *J*=9.0 and 11.2 Hz, CHSe), 3.08 (m, 1H, NCH), 2.51 (s, 3H, NMe), 2.43 (d, 1H, *J*=7.7 Hz, Hb), 1.81 (m, 3H), 1.27 and 1.48 (2×m, 4H), 1.06 (s, 3H, Me_a) and 0.99(m, 1H).

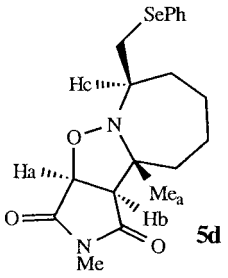


4d

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		11.0		
Hb	13			5.0
Me_a		4.8		

5d. Obtained as colourless fine needles from ethyl acetate–hexane, mp 124–125°C. (found: C, 56.1; H, 6.0; N, 6.8 $C_{19}H_{24}N_2O_3Se$ requires C, 55.9; H, 5.9; N, 6.9%). *m/z* (%) 408(M+1, 2), 237(100), 200 (5), 157 (18), 140(68), 111 (7), 77(19) and 41 (39). ν_{max} (nujol): 2990, 1850, 1680, 1420, 1340, 1260, 1120, 1000, 960, 840, 720 and 670 cm^{-1}. δ (400 MHz) (C_6D_6): 7.55 (m, 2H, ArH), 7.03 (m, 3H, ArH), 4.09 (d, 1H, *J*=7.9 Hz, Ha), 3.37 (dd, 1H, *J*=3.3 and 12.2 Hz, CHSe), 3.06 (m, 1H, NCH), 2.89 (dd, 1H, *J*=8.4 and 11.9 Hz, CHSe), 2.64 (s, 3H, NMe), 2.50 (d, 1H, *J*=7.9 Hz, Hb), 1.76 (m, 1H), 1.48 (m, 3H), 1.33 (m, 1H), 1.24 (s, 3H, Me_a), and 1.09 (m, 1H).



5d

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc
Ha		8.0	
Hb	14.0		

Reaction of oxime 1a with PhSeCl–AgOTf

A suspension of PhSeCl (0.34 g, 1.76 mmol) and AgOTf (0.45 g,1.76 mmol) in dry dichloromethane (10 mL) was stirred at 0°C in the dark. After 10 min. **1a** (0.2 g, 1.76 mmol) was added and the reaction mixture stirred at rt for 3 h. K_2CO_3 (1.24 g, 1.76 mmol) was then added and stirring continued at rt for a further 16 h The mixture was then filtered and the filtrate evaporated under reduced pressure to give a thick oil which was chromatographed on a short column of kieselgel to give nitrone **6a** (0.24 g, 51%) and oxazine **3a** (0.12 g, 25%).

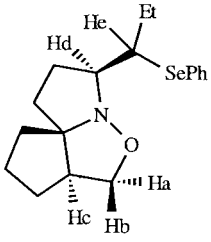
Oxazine 3a. Identical to that reported previously.[8] (Found: C, 54.0; H, 5.4; N, 4.9. $C_{12}H_{15}NOSe$ requires C, 53.74; H, 5.59; N, 5.22%). *m/z* (%) 269 (M^++1, 37), 252 (5), 112(100), 91 (75) and 43 (85). δ: 7.52 (m, 2H, ArH), 7.25 (m, 3H, ArH), 3.76 (m, 1H, OCH), 3.25 (dd, 1H, *J*=12.6 and 4.8 Hz, C*H*HSePh), 2.91 (dd, 1H, *J*=12.6 and 8.1 Hz, CH*H*SePh), 2.16 (m, 3H), 1.89 (s, 3H, Me and 1.48 (m, 1H).

Nitrone 6a. Identical to that reported previously.[8] (Found: C, 53.4; H, 5.4; N, 4.95. $C_{12}H_{15}NOSe$ requires C, 53.74; H, 5.59; N, 5.22%). *m/z* (%) (FAB) 269 (M^++1, 100) and 112(20). δ: 7.58 (m, 2H, ArH), 7.26 (m, 3H, ArH), 4.28 (m, 1H, NCH), 3.6 (dd, 1H, *J*=12.7 and 3.3 Hz, C*H*HSePh), 3.24 (dd, 1H, *J*=12.7 and 8.1 Hz, CH*H*SePh), 2.6 (m, 2H), 2.29 (m, 1H), 1.98 (s, 3H, Me), and 1.9 (m, 1H).

3-(1-Phenylselenyl-methyl)-hexahydro-cyclopenta[*c*]-pyrrolo[1,2-*b*]isoxazole (11). A solution of deca-1,9-dien-5-one oxime 8 (0.2 g, 1.20 mmol) and PhSeBr (0.28 g, 1.20 mmol) in dry CH_3CN (10 mL) was stirred at room temperature for 2 h. Anhydrous K_2CO_3 (0.2 g, 1.43 mmol) was then added and stirring continued for a further 10 min before the reaction mixture was boiled under reflux for 6 h. After cooling the solvent was removed under reduced pressure to leave a viscous yellow brown oil. The residue was purified by Kieselgel column chromatography, eluting with 1:1 v/v diethyl ether–hexane to afford the *product* **11** (0.14 g, 35%) as a colourless viscous oil. (Found: C, 59.9; H, 6.7; N, 4.3. $C_{16}H_{21}NOSe$ requires C, 59.6; H, 6.5; N, 4.4%). *m/z* (%) 323 (M^++1, 100), 269 (6), 224(7), 210 (6), 152 (55) and 134 (6). ν_{max} (nujol): 3060, 2940, 2860, 1580, 1470, 1435, 1320, 1290, 1020, 920, 730 and

685 cm^{-1}. δ (400 MHz): 7.48 (m, 2H, ArH), 7.22 (m, 3H, ArH), 4.05 (dd, 1H, *J*=6.6 and 8.9 Hz, Ha), 3.61(dd, 1H, *J*=2.6 and 8.9 Hz, Hb), 3.28(m, 2H, Hd and CHSe), 2.91 (m, 1H, CHSe), 2.47 (m, 1H, Hc), 1.98 (m, 4H), 1.77 (m, 2H) and 1.58 (m, 4H).

3-(1-Phenylselenyl-propyl)-hexahydro-cyclopenta[*c*]pyrrolo[1,2-*b*]isoxazole (17). A solution of dodeca-1,9-dien-6-one oxime **15** (0.1 g, 0.43 mmol) and PhSeBr (0.1 g, 0.43 mmol) in dry CH_3CN (10 mL) was stirred at room temperature for 2 h. Anhydrous K_2CO_3 (0.06 g, 0.45 mmol) was then added and stirring continued for a further 1 h before the reaction mixture was boiled under reflux for 5 h. After cooling the solvent was removed under reduced pressure to leave a viscous yellow brown oil. The residue was purified by Kieselgel column chromatography, eluting with 6:1 v/v petroleum ether–diethyl ether, to afford the *product* (0.09 g, 61%) as a colourless viscous oil which comprised a single stereoisomer. (Found: C, 61.9; H, 7.2; N, 4.0. $C_{18}H_{25}NOSe$ requires C, 61.6; H, 7.1; N, 4.0%). *m/z* (%) 351 (M^++1, 14), 194(27), 152(100), 134 (6), 93 (12)77 (14), 55 (16) and 41 (29). ν_{max} (nujol): 3080, 2960, 2880, 1590, 1490, 1440, 1380, 1340, 1130, 920, 840, 740 and 700 cm^{-1}. δ: 7.54 and 7.26 (2×m, 5H, ArH), 4.00 (t, 1H, *J*=7.2 Hz, Ha), 3.59 (d, 1H, *J*=7.9 Hz, Hb), 3.34 (m, 1H, Hd), 3.26 (m, 1H, He), 2.45 (m, 1H, Hc), 1.58, 1.78, 2.04 and 2.06 (4×m, 12H) and 1.05 (t, 3H, *J*=7.3 Hz, Me).

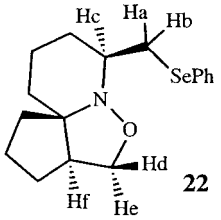


17

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Hd	He	Ph
Ha		27.3	6.9	9.2		
Hb	25.2					
Hc	2.5					
Hd	7.7					
He						8.7

4-Methyl-7-phenylselenylmethyl-octahydro-cyclopenta-[3,4] isoxazolo[2,3-*a*]pyridine (22). PhSeBr (0.13 g, 0.55 mmol) was added to a stirred solution of oxime **19** (0.1 g, 0.55 mmol) in dry dichloromethane (10 mL) and the mixture stirred at rt for 0.5 h to give the nitrone salt quantitatively. Anhydrous K_2CO_3 (0.73 g, 0.55 mmol) was added and the reaction mixture was stirred at room temperature for 16 h to generate the nitrone. The inorganic salt were filtered and the dichloromethane removed under reduced pressure and the residue was taken up in dry CH_3CN (10 mL) and the solution heated at 80°C for 5 h. After cooling the solvent was removed under reduced pressure and the residue was purified by Kieselgel column chromatography eluting with 1:1 v/v petroleum ether–diethyl ether to give to give the *product* (0.065 g, 65% yield) as a colourless thick oil (Found: C, 60.85; H, 6.95; N, 3.95. $C_{17}H_{23}NOSe$ requires C, 60.7; H, 6.84; N, 4.16%). *m/z* (%) 336 (M^+, 45), 192 (23), 91 (56) and 41 (40). δ: (C_6D_6): 7.5 (d, 2H, *J*=6.8 Hz, ArH), 6,97 (m, 3H, ArH), 3.8 (t, 1H, *J*=8.7 Hz, He), 3.66 (dd, 1H, *J*=12.3 and 2.76 Hz, Ha), 3.15 (dd, 1H, *J*=8,7 and 4.07 Hz, Hd), 2.90 (dd, 1H, *J*=12.3 and 8.7 Hz, Hb), 2.55 (m, 1H, Hc), 2.17 (m, 1H), 2.05 (m, 1H, Hf), 1.9 (m, 1H) and 1.68–0.84 (m, 10H).



22

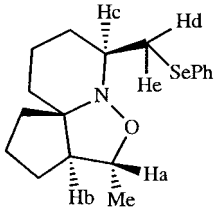
Enhancement (%)

Irradiated hydrogen	Hc	Hd	He	Hf
Hc				3.9
He	8.7	24		6.3
Hf	4.8			

7-Phenylselenylmethyl-octahydro-cyclopenta[3,4]isoxazolo[2,3-*a*]pyridine (29) and 7-(1-phenylselenylethyl-octahydro-cyclopenta[3,4]isoxazolo[2,3-*a*]pyridine (30)

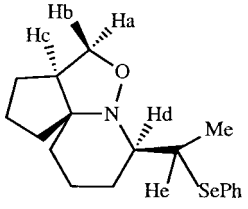
A solution of dodeca-1,10-dien-6-one oxime **24** (0.2 g, 1.02 mmol) and PhSeBr (0.24 g, 1.02 mmol) in dry CH_3CN (10 mL) was stirred at room temperature for 2 h. Anhydrous K_2CO_3 (0.15 g, 1.02 mmol) was then added and stirring continued for a further 1 h before the reaction mixture was boiled under reflux for 4 h. After cooling the solvent was removed under reduced pressure to leave a viscous yellow brown oil. The residue was purified by Kieselgel column chromatography, eluting with 6:1 v/v petroleum ether–diethyl ether to afford the *products* **29** (0.18 g, 47%) and **30** (0.09 g, 25%) as colourless viscous oils.

29. (Found: C, 61.6; H, 7.3; N, 4.1. $C_{18}H_{25}NOSe$ requires C, 61.6; H, 7.1; N, 4.0%). *m/z* (%) 351(M−1, 6), 180 (100), 157 (6), 91 (15), 77 (10), 55 (13) and 41 (19). δ (400 MHz): 7.51 (m, 2H, ArH), 7.21 (m, 3H, ArH), 3.69(m, 1H, Ha), 3.46 (m, 1H, Hd), 2.88 (m, 2H, Hc and He), 2.14 (t, 1H, *J*=6.7, Hz, Hb), 2.01 (m, 4H), 1.52, 1.56 and 1.66 (3×m, 7H), 1.44 (m, 1H) and 1.20 (d, 3H, *J*=6.7 Hz, Me).



29

30. (Found: C, 61.8; H, 7.4; N, 4.2. $C_{18}H_{25}NOSe$ requires C, 61.6; H, 7.1; N, 4.0%). *m/z* (%) 351(M−1, <1), 194 (1), 166 (100), 55 (5) and 41 (5). ν_{max} (nujol): 3020, 2920, 2860, 1570, 1470, 1430, 1370, 1200, 1030, 930, 900, 730 and 690 cm^{-1}. δ: 7.81 (m, 2H, ArH), 7.06 (m, 3H, ArH), 4.10 (t, 1H, *J*=8.7 Hz, Ha), 3.87 (m, 1H, He), 3.28 (dd, 1H, *J*=4.2 and 8.6 Hz, Hb), 2.62 (m, 1H, Hd), 2.24 (m, 1H, Hc), 1.70 (m, 1H), 1.52 (m, 3H), 1.51 (d, 3H, *J*=7.2 Hz, Me), 1.42 (m, 4H) and 1.01 and 1.31 (2×m, 2×2H).



30

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Hd	He
Ha		24.2	5.7	8.0	
Hb	21.1				
Hc	3.1			1.4	
Hd	6.9				8.1
He				6.1	

Acknowledgements

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