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# Stereoselective electrophile-induced mono- and bis-cyclisation–fragmentation reactions of alkenyl oxime *O*-allyl and *O*-benzyl ethers. Synthesis of dihydropinidine

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**Abstract**—Phenylseleny bromide-induced cyclisation of γ- and δ-unsaturated aldoxime and ketoxime *O*-allyl and *O*-benzyl ethers is followed by a slow fragmentation of the resultant oxyiminium ions furnishing cyclic iminium salts which are readily reduced to pyrrolidines, piperidines or tetrahydroisoquinolines by sodium borohydride; dialkenyl oximes yield indolizidines and quinolizidines by an analogous sequence terminating in a mercury(II)-induced cyclisation. 

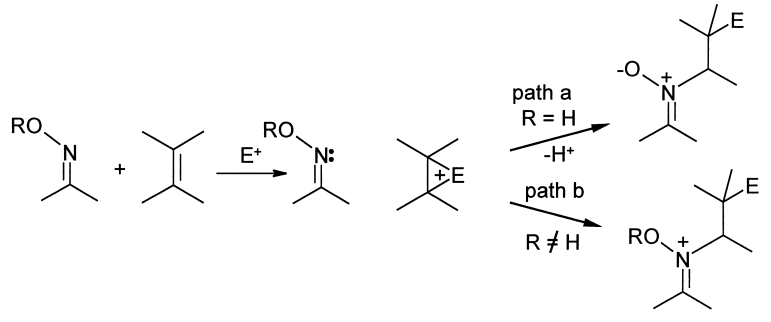
Recently, we have developed a range of electrophile-induced oxime–alkene reactions furnishing nitrones and their salts (Scheme 1, path a) in good to excellent yields.[1–3] In a preliminary communication, we reported a related electrophile-induced cyclisation of oxime *O*-allyl and *O*-benzyl ethers onto proximate alkenes generating the corresponding oxyminium ether salts (Scheme 1, path b). These oxyiminium ions can, under appropriate conditions, be transformed into nitrones, imines or, by reduction, hydroxylamines.[4] In recent papers, we reported Mannich reactions and Grignard chemistry of acyclic oxyiminium ions[5] and their application to the solid phase synthesis of tertiary amines.[6] We now report full details of our work with cyclic oxyiminium ions.

## 1. Cyclisation onto acyclic terminal alkenes

### 1.1. Monocyclisation of acyclic oxime ethers

Aldoxime ether **1** reacts rapidly with phenylseleny bromide (1 mol equiv.) in acetonitrile at room temperature to give salt **2**. Keeping the reaction mixture at room temperature for 18 h results in fragmentation **2**→**3** and subsequent reduction (2 equiv. $NaBH_4$, 1:1 v/v MeOH–$CH_2Cl_2$) of **3** gives **4** in 79% overall yield from **1** (Scheme 2).

A similar sequence starting from **5a** affords **7** which upon acetylation ($Ac_2O$, 25°C, 1.5 h) affords **8** in 64% overall yield from **5a**. The reaction was also carried out on **5b**




**Scheme 1.**

*Keywords*: iminium ions; oxyiminium ions; *endo*- and *exo*-trig cyclisation; cycloalkenes; *exo*-methylene cycloalkanes; onium ions.

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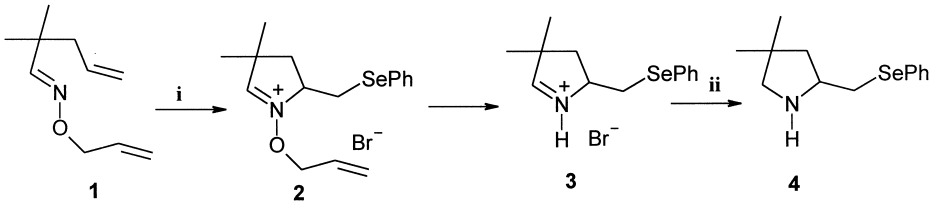
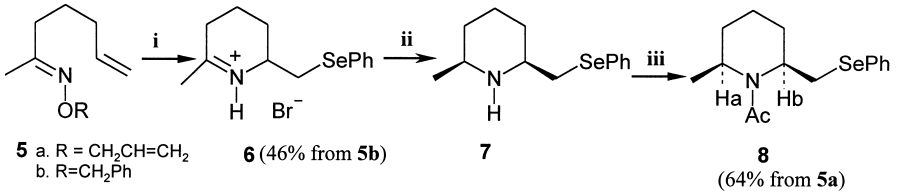


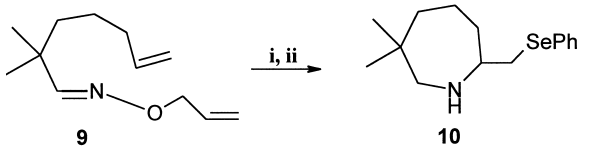

**Scheme 2.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$–$CH_2Cl_2$ (79% two steps).




**Scheme 3.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$–$CH_2Cl_2$; (iii) $Ac_2O$.

affording iminium salt **6b**, which was isolated and characterised in 46% yield. The 2,6-*cis* stereochemistry of **8** was established from n.O.e. data. Thus irradiation of $H_a$ ($\delta$ 3.2) effects a 6.4% enhancement of the $H_b$ proton signal at ($\delta$ 2.9) (Scheme 3).

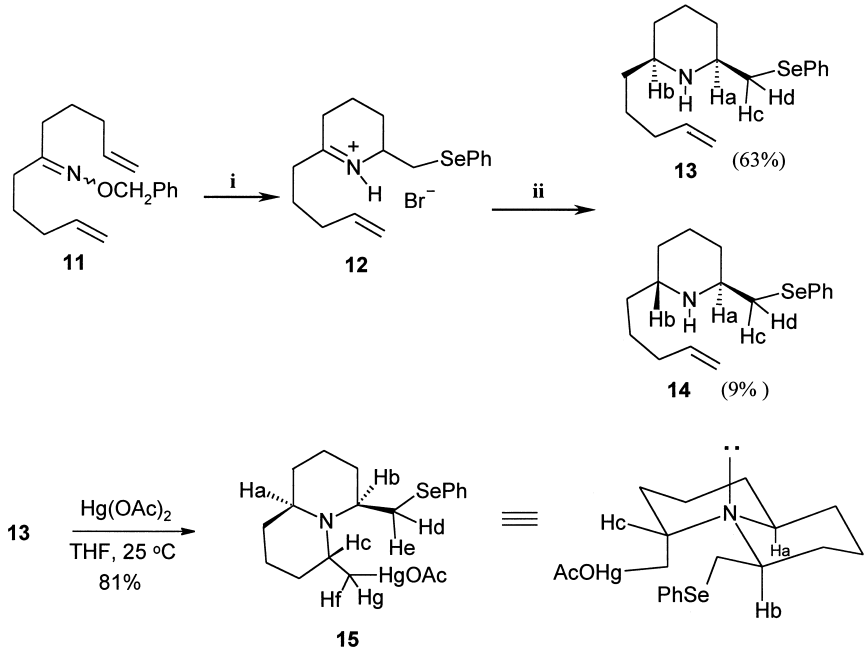
The efficacy of our general strategy for the synthesis of 7-membered rings was demonstrated by cyclisation of **9** which gave the perhydroazepine **10**, after fragmentation and reduction, in 52% overall yield from **9** (Scheme 4).



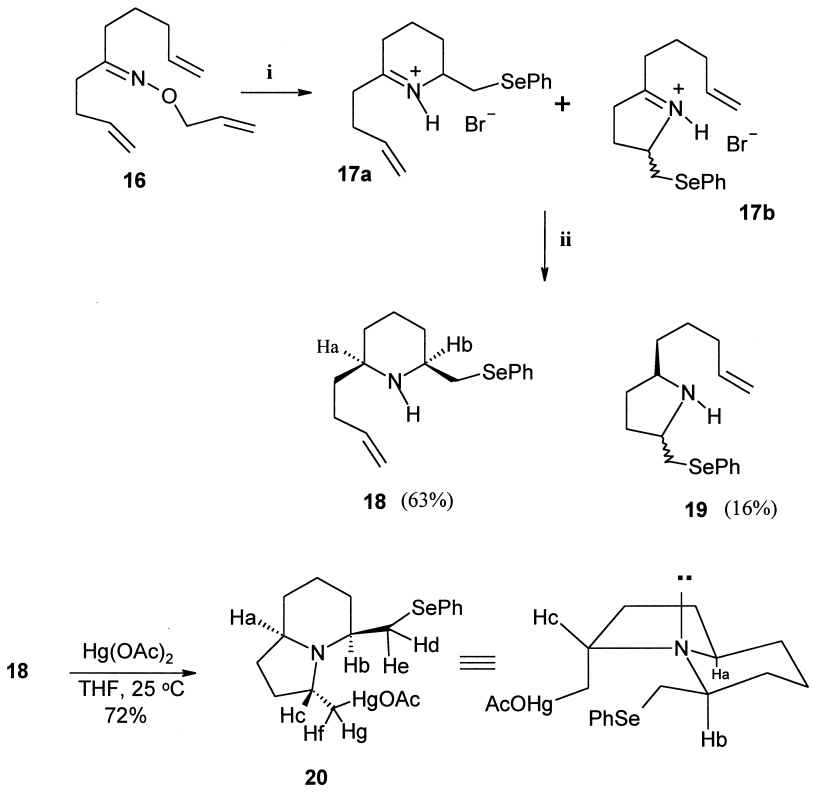

**Scheme 4.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$–$CH_2Cl_2$ (52%).

## 1.2. Sequential bicyclisation of cyclic oxime ethers

The symmetrical dialkenyl ketoxime **11**[7] was subjected to an analogous sequence of reactions and underwent the cyclisation–fragmentation sequence furnishing the salt **12**. Sodium borohydride reduction of **12** afforded a mixture of piperidines **13** (63%) and **14** (9%). The potential synthetic utility of dialkenyl oxime ethers is illustrated by mercuric acetate induced stereospecific cyclisation of **13** to quinolizidine **15** (81%). The stereochemistry of **15** is based on n.O.e. and decoupling data. Thus, irradiation of Ha results in a positive n.O.e on $H_b$ and $H_f$. Whilst irradiation of $H_c$ results in a positive n.O.e on $H_d$/$H_e$. Additionally, the chemical shifts of $H_a$ ($\delta$ 2.74) and $H_b$ ($\delta$ 2.75) are upfield relative to $H_c$ ($\delta$ 3.23) implying that $H_a$ and $H_b$ are *trans* to the nitrogen lone pair and axially orientated whereas $H_c$ is *gauche* to the lone pair and therefore equatorial (Scheme 5).




**Scheme 5.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$.



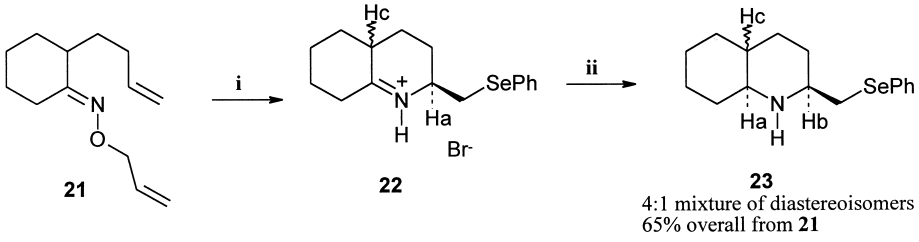

**Scheme 6.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$.

Another example is provided by the dialkenyl ketoxime *O*-allyl ether[8] **16** which underwent the cyclisation–fragmentation sequence furnishing a 4:1 mixture of salts **17a**,**b**. Electrophile-induced cyclisation of the oxime corresponding to **16** produced a 5:2 mixture of the 5-membered nitrone (corresponding to **17b**) and 6-membered nitrone (corresponding to **17a**).[1a] The reversal in selectivity for the 5-versus the 6-membered product in the case of the *O*-allyl oxime ethers presumably reflects the increased steric effect of the allyl moiety on the more rigid and crowded 5-membered transition state. Reduction of the mixture of salts gave, on isolation via chromatography, the piperidine **18** (63%) and the pyrrolidine **19** (16%). The stereochemistry of **18** was established from n.O.e studies. Irradiation of $H_a$ ($\delta$ 2.6) effects an 8.9% enhancement on $H_b$ ($\delta$ 2.3). The mercuric acetate induced stereospecific cyclisation of **18** to the indolizidine **20** was conducted in THF at room temperature and occurred in 72% yield. The stereochemistry of **20** was unequivocally established from n.O.e studies. Irradiation of $H_a$ ($\delta$ 2.4) effects a 3.4% enhancement of $H_b$ ($\delta$ 2.7) and a 2.1% enhancement on $H_f$ ($\delta$ 2.2). Whilst irradiation of $H_c$ ($\delta$ 3.2) effects a 4.6% enhancement on $H_d$ ($\delta$ 3.35) and 2.8 enhancement of $H_e$ ($\delta$ 3.0). Additionally, the chemical shifts of $H_a$ ($\delta$ 2.4) and $H_b$ ($\delta$ 2.7) are upfield relative to $H_c$ ($\delta$3.2) implying that $H_a$ and $H_b$ are *trans* and axial to the nitrogen lone pair whilst $H_c$ is *gauche* to the lone pair and therefore equatorial (Scheme 6).

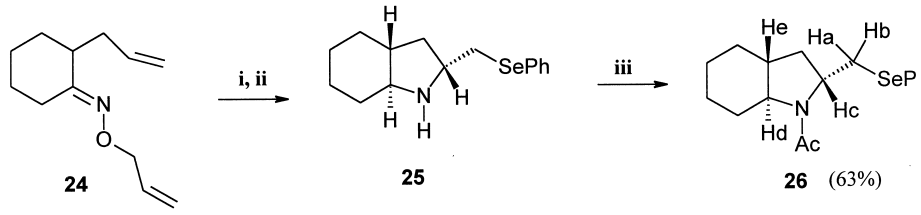
### 1.3. Monocyclisation of cyclic ketoxime ethers

Ketoxime[9] **21** undergoes a similar sequence to furnish **22** as a 4:1 mixture of *trans*- and *cis*-diastereoisomers ($H_a/H_c$) respectively. Reduction of **22** with $NaBH_4$ gives **23** [65% overall from **21** as a 4:1 mixture of diastereomers. The stereochemistry of both these diastereomers was established from n.O.e data ($C_6D_6$). Irradiation of $H_c$ ($\delta$ 2.05) in the *cis* isomer effects a 9.2% enhancement of $H_b$ ($\delta$ 2.95). Irradiation of $H_c$ ($\delta$ 2.0) in the *trans*-isomer effects no enhancement on $H_b$ ($\delta$ 2.65) (Scheme 7).

The cyclisation–reduction sequence was repeated using ketoxime[9] **24** which affords **25** as a single stereoisomer. Subsequent acetylation ($Ac_2O$, 25°C, 16 h) afforded **26** in 63% overall yield from **24**. The relative stereochemistry of

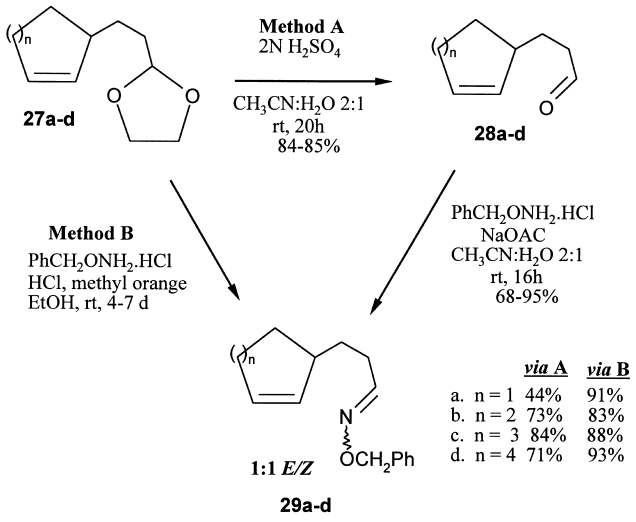



**Scheme 7.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$–$CH_2Cl_2$.




**Scheme 8.** (i) PbSeBr, $CH_3CN$, $N_2$; (ii) $NaBH_4$, $CH_3OH$–$CH_2Cl_2$; (iii) $Ac_2O$.

$H_c$, $H_d$ and $H_e$ was established by n.O.e. studies. Irradiation of proton $H_e$ ($\delta$ 1.8) effects a 6.3% enhancement of the $H_c$ proton signal ($\delta$ 4.3); whilst irradiation of $H_d$ ($\delta$ 3.1) effects a 3.1% enhancement of Hb ($\delta$ 2.75) and a 1.4% enhancement of $H_a$ ($\delta$ 4.25) (Scheme 8).

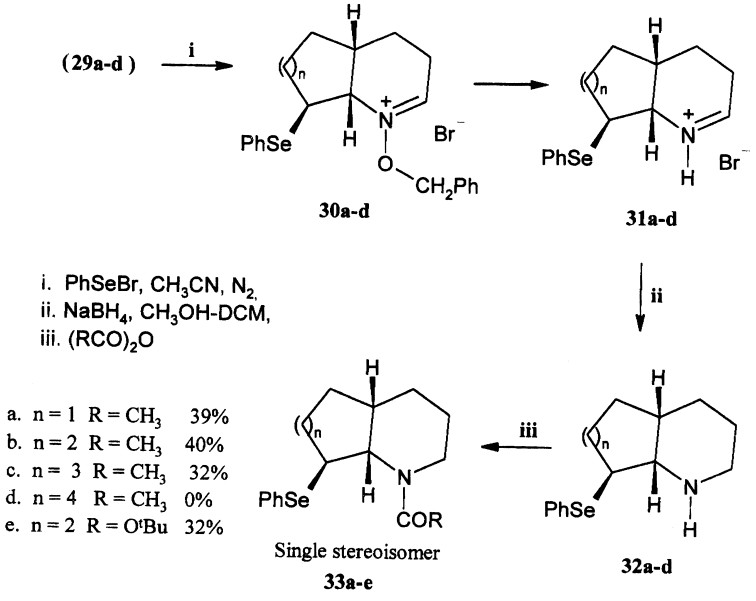



**Scheme 9.**

## 2. Cyclisation of acyclic oxime ethers onto endocyclic alkenes

The synthesis of oxime *O*-benzyl ethers **29a–d** was achieved as outlined in Scheme 9 using two different methods, A and B, starting from unsaturated acetals **27a–d** or unsaturated aldehydes **28a–d**.

1:1 Mixtures of *E*- and *Z*- isomers of oxime *O*-benzyl ethers **29a–d** react rapidly with phenylselenyl bromide (1 equiv.) in $CH_3CN$ at room temperature via 6-*exo*-trig cyclisation to give bicyclic *cis*-fused oxyiminium salts **30a–d** (Scheme 10). Keeping the reaction mixture at room temperature for 16 h resulted in fragmentation to the iminium salts **31a–d**. Reduction of the iminium salts with $NaBH_4$ affords bicyclic piperidines **32a–d** as a single stereoisomers. The piperidines were directly converted into amides using acetic anhydride or di-*tert*-butylcarbonate. Amides **33a–c** and **33e** were obtained as single stereoisomers, which comprised a 1:1 or 2:1 mixture of amide bond rotamers ($^1$H NMR) but the broadness of the $^1$H NMR signals prevented measurement of the coupling constants, making the assignment difficult. Aldoxime **29d** failed to undergo the cyclisation–fragmentation. In this case, molecular models suggest that conformational factors create some steric hindrance on one face of olefin which impedes attack of either the electrophile on the double bond or attack of the nitrogen lone pair on the selenonium ion.




**Scheme 10.**

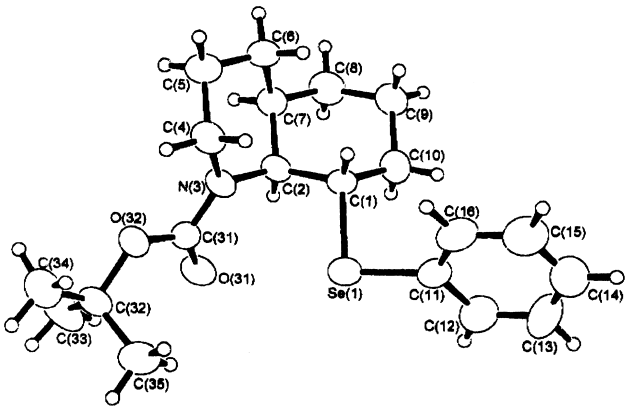



**Figure 1.** X-ray crystal structure of **33a**.

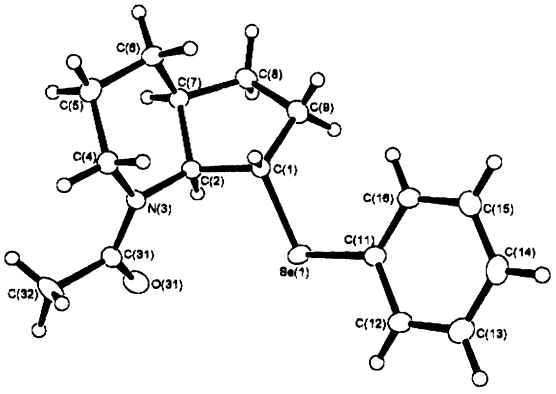



**Figure 2.** X-ray crystal structure of **33e**.

The yields of **33a–c** and **33e** are the overall yields for 4 steps (cyclisation, fragmentation, reduction and acetylation) and they correspond to an average yield of 75–80% per step. The *cis*-ring junction stereochemistry of amides **33a** and **33e** was determined by X-ray crystallography (Figs. 1 and 2). The stereochemistry of amides **33b** and **33c** are assigned by analogy.

## 3. Cyclisation of *O*-benzyl oxime ethers onto *exo*-methylene alkenes

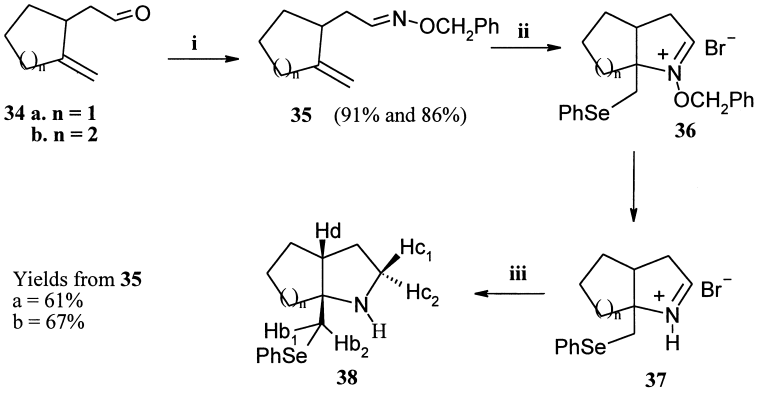
The aldehydes **34a**,**b**[10] were converted to 2:1 mixtures of *E*/*Z* isomers of *O*-benzyl ethers **35a** and **35b** in 91 and 86% yield, respectively. The aldoxime ethers **35a**,**b** reacted with phenylselenyl bromide (1 mol equiv.) in $CH_3CN$ at room temperature to give oxyiminium salts **36a**,**b**. Keeping the reaction mixture at room temperature for 16 h resulted in fragmentation of **36a**,**b** to the iminium salts **37a**,**b**. Reduction (2 mol equiv. $NaBH_4$, 1:1 v/v MeOH–$CH_2Cl_2$, 25°C, 1 h) of **37a**,**b** gave **38a,b** as single stereoisomers in 61 and 67% overall yield, respectively from **35ab**. The stereochemistry of **38b** was established from n.O.e and 2D-COSY studies. Irradiation of $H_{b1}$ ($\delta$ 3.5) effects a 20% enhancement of $H_{b2}$ ($\delta$ 3.1) and irradiation of $H_{b2}$ effects a 22% enhancement of $H_{b1}$ and 2.0% enhancement of $H_d$ ($\delta$ 2.5), irradiation of $H_{c1}$ ($\delta$ 1.95) effects a 21% enhancement on $H_{c2}$ ($\delta$ 1.66) and 7.8% enhancement of $H_d$ and irradiation of $H_d$ effects a 1.7% enhancement of $H_{b1}$ and a 1.9% enhancement of $H_{b2}$ (Scheme 11).

## 4. Synthesis of (±)-dihydropinidine

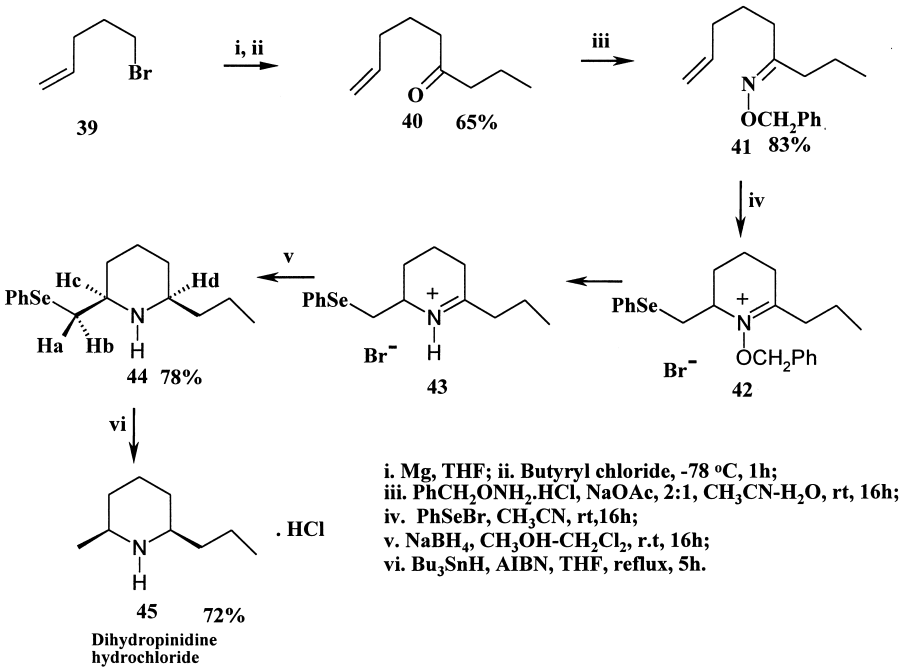
Dihydropinidine **45** has been isolated from several pine species[11] and from the Mexican bean beetle.[12] It is highly teratogenic and embryotoxic.[13] Several syntheses of dihydropinidine, including chiral syntheses have been reported.[13–18]

We have exemplified our methodology by devising a 6-step synthesis of this alkaloid in 42% overall yield (Scheme 12) from 5-bromopent-1-ene. 5-Bromopent-1-ene **39** converted into the corresponding Grignard reagent and reacted with butyryl chloride at −78°C for 1 h to give the unsaturated ketone **40** in 65% yield.[19] The ketone reacted with *O*-benzylhydroxylamine hydrochloride in the presence of sodium acetate at room temperature over 16 h to give the oxime ether **41** as a 1:1 mixture of *E*/*Z* isomers in 83% yield (Scheme 12).

The oxime ether **41** reacted with phenylselenyl bromide in acetonitrile at room temperature to give the corresponding oxyiminium salt **42**. Keeping the solution at room temperature for 16 h resulted in fragmentation to the iminium salt **43**, which was then reduced using sodium borohydride at room temperature for 16 h to give the *cis*-2,6-disubstituted piperidine **44**, stereospecifically, in 78% overall yield from the oxime ether **41**. The stereochemistry of piperidine **44** was determined on the basis of n.O.e data and 2D-COSY studies. Removal of the PhSe group was effected by




**Scheme 11.** (i) $PhCH_2ONH_2{\cdot}HCl$, $CH_3COONa$, $CH_3CN/H_2O$; (ii) PhSeBr, $CH_3CN$, $N_2$; (iii) $NaBH_4$, $CH_3OH$.




**Scheme 12.**

tributyltin hydride/AIBN in THF under reflux for 5 h. Removal of the PhSe group using tributyltin hydride in benzene or toluene gave poor yields (45 and 10%, respectively). Acidic work up afforded the dihydropinidine hydrochloride **45** in 72% yield. The spectroscopic properties (mp, $^1$H NMR and mass) of the synthetic alkaloid are identical with the literature data.[13]

## 5. Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. $^1$H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker DPX 300 instrument or at 400 MHz on a Bruker WP 400 instrument. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts ($\delta$) are referenced to tetramethylsilane or residual protonated solvent. Assignments of $^1$H signals were made with the aid of 2D COSY spectra where necessary. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Mass spectra were recorded on a VG-AutoSpec spectrometer using electron impact (EI) operating at 70 eV or by fast atom bombardment (FAB), as specified. Flash column chromatography employed silica gel 60 (Merk 230–400 mesh). Ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40–60°C. All reagents and solvents were purified according to literature procedures. 2,2-dimethyl-4-pentenal,[20] 2,2-dimethyl-6-hepten-1-ol[21] and non-8-en-4-one[19] were prepared by literature methods.

### 5.1. General procedure for oxime formation

$NH_2OH{\cdot}HCl$ (1.20 mmol) and NaOAC (1.50 mmol) were added to a stirred solution of the aldehyde (or ketone) (1.0 mmol) in 3:1 v/v $CH_3CN$–$H_2O$ (30 mL) at room temperature and stirring continued for 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

**5.1.1. 2,2-Dimethyl-4-pentenal oxime.** The product (83%) was obtained as a colourless liquid, bp 50–55°C/5 mm Hg. (Found: C, 75.6, H, 11.9, N, 12.6. $C_7H_{13}NO$ requires: C, 75.6, H, 11.8, N, 12.6%); $\delta$ 8.6 (brs, 1H, NOH), 7.3 (s, 1H, CH=N), 5.85 (m, 1H, *CH*=$CH_2$), 5.05 (m, 2H, $CH_2$=CH), 2.2 (d, 2H, $J$=7.5 Hz, $CH_2$CH=$CH_2$) and 1.1 (s, 6H, 2×Me).

### 5.2. General method for the preparation of oxime *O*-allyl ethers

Potassium carbonate (1 mol equiv.) and allyl bromide (1 mol equiv.) were added to a solution of oxime in acetonitrile. The resulting solution was stirred at 80°C for 4–5 h. The acetonitrile was then removed under reduced pressure and the residue partitioned between chloroform and water. The chloroform extract was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residual oil was purified by column chromatography on silica or by distillation.

### 5.3. General method for the preparation of oxime *O*-benzyl ethers

A solution of aldehyde (1 mol equiv.) in acetonitrile was added to a solution of *O*-benzylhydroxylamine hydrochloride (1 mol equiv.) and sodium acetate (1.2 mol equiv.) in water. The resulting solution was stirred at ambient

temperature for 8 h, and then extracted with chloroform (2×). The combined organic layer was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was subjected to column chromatography on silica, eluting with petroleum ether–ether.

**5.3.1. 2,2-Dimethyl-4-pentenal oxime *O*-allyl ether 1.** Prepared from the oxime using allyl bromide. The product (76%) was obtained as a colourless oil, bp 30–42°C/0.4 mm Hg. (Found: C, 71.8; H, 10.45; N, 8.45. $C_{10}H_{17}NO$ requires: C, 71.8; H, 10.25; N, 8.35.%); $\delta$ 7.35 (s, 1H, CH═N), 6.0 (m, 1H, $OCH_2CH$═$CH_2$), 5.8 (m,1H, $CH$═$CH_2$), 5.25 (m, 2H, $OCH_2CH$═$CH_2$), 5.05 (m, 2H, $CH_2$═CH), 4.55 (d, 2H, $J$=5.5 Hz, $OCH_2$), 2.0 (d, 2H, $J$=7.5 Hz, $CH_2CH$═$CH_2$) and 1.1 (s, 6H, 2×Me); *m/z* (%) 167 ($M^+$, 10) and 95 (100).

**5.3.2. 4,4-Dimethyl-2-[(phenylseleno) methyl pyrrolidine 4.** *O*-Allyl ether **1** (500 mg, 2.99 mmol) was added to a stirred suspension of phenylselenyl bromide (705 mg, 2.99 mmol) in dry acetonitrile (20 mL) at room temperature under a nitrogen atmosphere. Instant decolouration of the suspension took place. After 18 h, the salt **3** was obtained after removal of solvent under reduced pressure. Without purification, the crude salt was reduced over 18 h by addition to a stirred mixture of sodium borohydride (2 mol equiv.) in 1:1 v/v methanol–dichloromethane (25 mL) at room temperature over 18 h. The residue was purified by column chromatography, eluting with 1:1 v/v ether–petroleum ether, to give a thick colourless oil (634 mg, 79% overall from **1**). (Found: C, 58.0, H, 7.15, N, 5.3. $C_{13}H_{19}NSe$ requires: C, 58.2, H, 7.15, N, 5.2%); $\delta$ 7.20–7.50 (m, 5H, ArH), 3.35 (m,5H, NCH, $CH_2SePh$ and $NCH_2$), 3.00–1.40 (m, 2H, $NCHCH_2$) and 1.10 (s, 6H, 2×Me). *m/z* (%) 268 ($M^+$, 13) and 112 (100).

**5.3.3. Methyl 5-hexenyl ketoxime *O*-allyl ether 5a.** Prepared from the oxime using allyl bromide. The product (75%) was obtained as a colourless oil, bp 78–84°C/5 mm Hg. (Found: C, 71.7, H, 10.05, N, 8.25. $C_{10}H_{17}NO$ requires: C, 71.8, H, 10.25, N, 8.35%); $\delta$ 6.00 (m, 1H, $OCH_2CH$═$CH_2$), 5.80 (m, 1H, $CH$═$CH_2$), 5.25 (m, 2H, $CH_2$═CH), 5.00 (m, 2H, $CH_2$═$CH$), 4.60 (m, 2H, $OCH_2$), 1.90 (s, 3H, Me) and 1.60–2.20 (m, 6H, 3×$CH_2$); *m/z* (%) 167 ($M^+$, 32) and 95 (48).

**5.3.4. Methyl 5-hexenyl ketoxime *O*-benzyl ether 5b.** The product (94%, 3:1 mixture of *E* and *Z* isomers) was obtained as a colourless oil, bp. 84°C/0.01 mm Hg. (Found: C, 77.45, H, 6.65, N, 8.7. $C_{14}H_{19}NO$ requires: C, 77.40, H, 6.45, N, 8.75%); $\delta$ 7.3 (m, 5H, ArH), 5.78 (m, 1H, $CH$═$CH_2$), 5.07 (s, 2H, $OCH_2Ph$), 4.99 (m, 2H, CH═$CH_2$), 2.36 and 2.17 (2×t, total 2H, $J$=8.0 Hz, *Z*- and *E*-$CH_2C$═N), 2.0 (q, 2H, $J$=7.5 Hz, $CH_2C$═$CH_2$), 1.85 (s, 3H, Me) and 1.7 (m, 2H, $CH_2$); *m/z* (%) 217 ($M^+$, 1), 200 (2), 163 (14), 111(27) and 91(100).

**5.3.5. Iminium bromide 6b.** Phenylselenyl bromide was added to a solution of **5b** (0.3 g, 1.38 mmol) in dry acetonitrile (15 mL) and the mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum to give a pale brown gum which crystallised from DCM–petroleum ether to give the product (0.22 g, 46%) as colourless rods. (Found: C, 44.85; H, 5.0; N, 3.95; Br, 23.15. $C_{13}H_{18}BrNSe$ requires: C, 44.95; H, 5.2; N, 4.05; Br, 23.05%); $\delta$ 7.6 (dd, 2H, $J$=7.5, 1.5 Hz, ArH), 7.3 (m, 3H, ArH), 4.0 (m, 1H, NCH), 3.88 (dd, 1H, $J$=13.5, 3.5 Hz, PhCH*H*), 3.21 (dd, 1H, $J$=13.5, 10.15 Hz, PhC*H*H), 2.7 (m, 2H), 2.6(s, 3H, Me), 2.17 (m, 1H), and 1.84 (m, 3H); *m/z* (%) 267 ($M^+$−Br, 32), 186 (100), 172 (43), 157 (29), 91 (48) and 77 (37).

**5.3.6. 1-Acetyl-2-methyl-6-[(phenylseleno)methyl]piperidine 8.** Oxime *O*-allyl ether **5a** (500 mg, 2.99 mmol) was added to a stirred suspension of phenylselenyl bromide (705 mg, 2.99 mmol) in dry acetonitrile (20 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 19 h. Removal of the solvent under reduced pressure gave the crude salt which was reduced with sodium borohydride (2 equiv.) in 1:1 v/v methanol–chloroform (25 mL) at room temperature over 18 h. Removal of the solvent under reduced pressure gave the crude piperidine which was extracted with dichloromethane and the solvent evaporated. The crude piperidine was then stirred in dry acetic anhydride (10 mL) at room temperature for 1.5 h to afford **8a**, which was purified by flash chromatography, eluting with ether to give the product as a colourless thick oil (64% overall from **5a**). (Found: C, 58.0; H, 6.9; N, 4.6. $C_{15}H_{21}NOSe$ requires: C, 58.05; H, 6.8; N, 4.5%); $\delta$ 7.60–7.30 (m, 5H, ArH), 3.80–4.80 (m, 2H, $CH_2SePh$), 3.15 (m, 1H, $H_a$), 2.90 (m, 1H, $H_b$), 2.20 (s, 3H, MeCO) and 1.70–1.10 (m, 9H, Me and 3×$CH_2$); *m/z* (%) 310 ($M^+$, 10), 267(55) and 154 (90).

**5.3.7. 2,2-Dimethyl-6-heptenal oxime *O*-allyl ether 9.** The oxime was prepared in the usual way from 2,2-dimethyl-6-heptenal in aqueous acetonitrile. Work up in the usual way gave the oxime which was then *O*-allylated without purification, by the general method using allyl bromide to give **9** (75%) as a colourless oil, bp 50–54°C/0.6 mm Hg. (Found: C, 73.7; H, 10.95; N, 7.0. $C_{12}H_{21}NO$ requires: C; 73.8, H, 10.85; N, 7.15%); $\delta$ 7.40 (s, 1H, CH═N), 6.00 (m, 1H, $OCH_2CH$═$CH_2$), 5.80 (m, 1H, $CH$═$CH_2$), 5.25 (m, 2H, $OCH_2CH$═$CH_2$), 5.00 (m, 2H, $CH_2$═CH), 4.50 (d, 2H, $J$=5.1 Hz, $OCH_2$), 2.00 (m, 2H, $CH_2CH$═$CH_2$) 1.40 (m, 4H, 2×$CH_2$) and 1.10 (s, 6H, 2×Me).

**5.3.8. 5,5-Dimethyl-2-[(phenylseleno)methyl]azepane 10.** Oxime *O*-allyl ether **15** (500 mg, 2.56 mmol) was added to a stirred suspension of phenylselenyl bromide (604 mg, 2.56 mmol) in dry acetonitrile (20 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 19 h. Removal of the solvent under reduced pressure gave the crude salt which was reduced sodium borohydride (2 equiv.) in 1:1 v/v methanol–chloroform (25 mL) at room temperature for 18 h. Work up followed by flash chromatography eluting with ether gave the product (394 mg, 52%) as a colourless thick oil. (Found: C, 60.9; H, 7.9; N, 4.8. $C_{15}H_{23}NSe$ requires: C, 60.8; H, 7.8; N, 4.75%); $\delta$ 7.50–7.30 (m, 5H, ArH), 3.70–3.10 (m, 4H, NH, $CHCH_2SePh$), 3.0–1.40 (m, 8H, 4×$CH_2$) and 1.10 (s, 6H, 2×Me); *m/z* (%) 296 (M−1, 11) and 140 (90).

**5.3.9. 1,10-Undecadien-6-one ketoxime *O*-benzyl ether 11.** The product (61%) was obtained as a colourless oil, bp 110°C/0.01 mm Hg. (Found: C, 79.2; H, 9.1; N, 4.9. $C_{18}H_{25}NO$ requires: C, 79.6; H, 9.2; N, 5.15%); $\delta$ 7.30

(m, 5H, ArH), 5.42 (m, 2H, 2×C*H*═$CH_2$), 4.85 (m, 6H, $OCH_2$ and 2×CH═C$H_2$), 2.31 (t, 2H, *J*=8.0 Hz, *Z*-$CH_2$C═N), 2.16 (t, 2H, *J*=7.9 Hz, *E*-$CH_2$C═N), 2.04 (m, 4H) and 1.57 (m, 4H,); *m/z* (%) 271 ($M^+$, 1), 256(1), 230(5), 111 (27) and 91 (100).

**5.3.10. *cis*-2-(4-Pentenyl)-6-[(phenylseleno)methyl]piperidine 13 and *trans*-2-(4-pentenyl)-6-[(phenylseleno)-methyl]piperidine 14.** Phenylselenyl bromide (0.87 g, 3.69 mmol) was added to a solution of oxime ether **11** (1 g, 3.69 mmol) in dry acetonitrile (10 mL). The resulting solution was stirred at room temperature for 16 h. Acetonitrile was removed under reduced pressure and the residue was taken up in DCM–MeOH (1:1 v/v) (10 mL), $NaBH_4$ (0.28 g, 7.38 mmol) added and the mixture stirred at room temperature for 1 h. The solvent was then evaporated under reduced pressure and the residue subjected to column chromatography on silica, eluting with ether to give **13** (0.78 g, 63%) and **14** (0.11 g, 9%) as colourless thick oils.

**5.3.11. Compound 13.** Found: C, 63.15; H, 8.05; N, 4.3. $C_{17}H_{25}NSe$ requires: C, 63.35; H, 7.76; N, 4.34%; δ 7.50 (m, 2H, ArH), 7.30 (m, 3H, ArH), 5.80 (m, 1H, C*H*═$CH_2$), 4.98 (m, 2H, CH═C$H_2$), 3.07 (m, 1H, $H_c$), 2.78 (dd, 1H, *J*=12.5, 9.5 Hz, $H_d$), 2.56 (m, 1H, $H_a$), 2.43 (m, 1H, $H_b$), 2.15 (m, 3H), 1.78 (m, 1H), 1.65 (m, 1H), 1.56 (m, 1H), 1.50–1.00 (m, 7H); *m/z* (%) 323($M^+$, 8), 254 (15), 166 (19), 152 (100) and 96 (47). $^1$H (NOEDS) irradiation of Ha caused enhancement of the signal for $H_b$ (1.3%) and irradiation of $H_b$ caused enhancement of the signal for $H_a$ (5.6%).

**5.3.12. Compound 14.** Found: C, 63.1; H, 7.75; N, 4.4. $C_{17}H_{25}NSe$ requires: C, 63.35; H, 7.76; N, 4.34%; δ 7.50 (d, 2H, *J*=7.5 Hz, ArH), 7.03 (t, 2H, *J*=7.5 Hz, ArH), 6.90 (t, 1H, *J*=7.0 Hz, ArH), 5.70 (m, 1H, C*H*═$CH_2$), 5.00 (m, 2H, CH═C$H_2$), 3.30 (dd, 1H, *J*=12.5, 5.5 Hz, $H_c$), 3.13 (m, 1H, $H_b$), 2.80 (m, 2H, $H_a$ and $H_d$), 1.90 (q, 2H, *J*=7.0 Hz), 1.70 (m, 1H), 1.46 (m, 3H) and 1.25–1.00 (m, 7H); *m/z* (%) 323 ($M^+$, 2), 254 (12), 166 (9), 152 (100) and 96 (43). $^1$H (NOEDS) irradiation of $H_a$ shows no enhancement of the signal for $H_b$ and irradiation of $H_b$ shows no enhancement of the signal for $H_a$.

**5.3.13. Compound 15.** Compound **13** (100 mg, 0.30 mmol) was added to a stirred solution of mercuric acetate (0.095 g, 0.3 mmol) in dry THF (10 mL) and stirring continued at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue triturated with ether to precipitate the product (0.14 g, 78%) which crystallised from DCM/petroleum ether as colourless prisms, mp 129–130°C. (Found: C, 38.7; H, 4.75; N, 2.5. $C_{19}H_{27}NO_2SeHg$ requires: C, 39.3; H, 4.5; N, 2.5%); δ 7.50 (m, 2H, ArH), 7.24 (m, 3H, ArH), 3.59 (m, 1H, $H_c$), 3.17 (dd, 1H, *J*=11.5, 6.5 Hz, $H_d$), 3.00 (dd, 1H, *J*=11.5, 2.0 Hz, $H_e$), 2.74 (m, 1H, $H_b$), 2.46 (m, 1H, $H_a$), 2.20 (t, 1H, *J*=11.0 Hz, $H_f$), 2.06 (m, 1H, $H_g$), 2.0 (s, 3H, OMe), 1.57 (m, 2H), 1.36 (m, 7H) and 1.26 (m, 3H); *m/z* (%) 580 (M−1, 8), 536(4), 378(90), 324 (100), 244 (80) and 152 (100). $^1$H (NOEDS) irradiation of $H_a$ caused enhancement of the signal for $H_b$ (2.1%) and $H_f$ (1.2%). Irradiation of $H_b$ caused enhancement of the signal for $H_a$ (1.8%). Irradiation of $H_c$ caused enhancement of the proton signals for $H_d$ (4.4%) and $H_e$ (4.5%).

**5.3.14. 5-Oxodeca-1.9-diene oxime *O*-allyl ether 16.** The product (64%) was obtained as a colourless oil, bp 90–94°C/0.7 mm Hg. (Found: C, 75.0; H, 10.0; N, 6.7. $C_{13}H_{21}NO$ requires: C, 75.3; H, 10.2; N, 6.75%); δ 6.0 (m, 1H, $OCH_2$C*H*═$CH_2$), 5.80 (m, 2H, 2×C*H*═$CH_2$), 5.25 (m, 2H, $OCH_2$CH═C$H_2$), 5.00 (m, 4H, 2×C$H_2$═CH), 4.55 (d, 2H, *J*=5.0 Hz, $OCH_2$) and 2.40–1.60 (m, 10H, 5×$CH_2$), *m/z* (%) 207 ($M^+$, 15), 1520(41), 138(58) and 136 (100).

**5.3.15. 2-(3-Butenyl)-6-[(phenylseleno)methyl]piperidine 18.** 5-Oxodeca-1.9-diene oxime *O*-allyl ether (500 mg, 2.41 mmol) was added to a stirred suspension of phenylselenyl bromide (569 mg, 2.41 mmol) in dry acetonitrile (20 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 19 h. Removal of the solvent under reduced pressure gave the crude salt which was reduced by addition to a stirred solution of sodium borohydride (2 equiv.) in 1:1 v/v methanol–chloroform (25 mL) at room temperature to give a 4:1 mixture of piperidine **18** and pyrrolidine **19**. The major product **18** (468 mg, 63%) was isolated as a colourless thick oil by flash chromatography eluting with ether. (Found: C, 62.1; H, 7.2; N, 4.3. $C_{16}H_{23}NSe$ requires: C, 62.35; H, 7.5; N, 4.55%); δ 7.50 (m, 2H, ArH), 7.00 (m, 3H, ArH), 5.75 (m, 1H, C*H*═$CH_2$), 5.00 (m, 2H, C$H_2$═CH), 2.90, 2.80 (2×m, 2H, C$H_2$SePh), 2.60 (m, 1H, $H_b$), 2.30 (m, 1H, $H_a$), 2.00 (m, 2H, C$H_2$CH═$CH_2$) and 1.60–1.00 (m, 9H, 4×$CH_2$ and NH); *m/z* (%) 308 (M−1, 5), 253 (32) and 152 (100).

**5.3.16. Compound 20.** Compound **18** (400 mg, 1.30 mmol) was added to a stirred solution of mercuric acetate (413 mg, 1.30 mmol) in dry THF (25 mL) and stirring continued at room temperature for 18 h under a nitrogen atmosphere. Work up as for **15** afforded the product (72%) as a colourless froth. (Found: C, 35.1; H, 4.6; N, 2.4. $C_{18}H_{25}NO_2SeHg$ requires: C, 35.4; H, 4.65; N, 2.6.%); δ 7.60–7.20 (m, 5H, ArH), 3.20 (m, 1H, $H_c$), 3.35, 3.00 (2×m, 2H, C$H_2$SePh), 2.70 (m, 1H, $H_b$), 2.40 (m, 1H, $H_a$), 2.20, 2.05 (2×m, 2H, $CH_2$HgOAc), 2.00 (s, 3H, Me) and 1.60–1.30 (m, 10H, 5×$CH_2$); *m/z* (%) 567 ($M^+$, 21), 386 (28) and 283 (100).

**5.3.17. 2-(3′-Butenyl) cyclohexanone oxime *O*-allyl ether 21.** Prepared from the oxime using allyl bromide. The product (81%) was obtained as a colourless oil, bp 67–70°C/3 mm Hg. (Found: C, 75.3; H, 10.2; N, 6.7. $C_{13}H_{21}NO$ requires: C, 75.3; H, 10.2; N, 6.75%); δ 6.00 (m, 1H, $OCH_2$C*H*═$CH_2$), 5.85 (m, 1H, C*H*═$CH_2$), 5.25 (m, 2H, $OCH_2$CH═C$H_2$), 5.00 (m, 2H, C$H_2$═CH), 4.55 (d, 2H, *J*=5.0 Hz, $OCH_2$), and 2.40–1.30 (m, 13H, 6×$CH_2$ and CH); *m/z* (%) 207 ($M^+$, 10), 166 (42) and 152 (100).

**5.3.18. 2-[(Phenylseleno)methyl]decahydroquinoline 23.** 2-(3′-Butenyl) oxime *O*-allyl ether **21** (500 mg, 2.41 mmol) was added to a stirred suspension of phenylselenyl bromide (569 mg, 2.41 mmol) in dry acetonitrile (20 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 19 h. Removal of the solvent under reduced pressure gave the crude salt **22** which, without purification, was reduced by addition to a stirred solution of sodium borohydride (2 equiv.) in 1:1 v/v methanol–chloroform (25 mL) at room temperature. Stirring was continued for 19 h. Work up afforded a 4:1 mixture of stereoisomers was purified by flash chromatography, eluting with ether

to give the pure isomers as colourless oils [360 mg, 65% overall from **21**].

**5.3.19. (Major) *trans*-isomer (23).** Found: C, 62.3; H, 7.6; N, 4.65. $C_{16}H_{23}NSe$ requires: C, 62.35; H, 7.5; N, 4.55%; $\delta$ $C_6D_6$) 7.50–7.30 (m, 5H, ArH), 3.30–3.10 (m, 2H, $CH_2SePh$), 3.00 (br, 1H, NH), 2.95 (m, 1H, $H_b$), 2.70 (m, 1H, $H_a$), 2.00 (m, 1H, $H_c$) and 1.85–1.00 (m, 12H, 6×$CH_2$); *m/z* (%) 308 (M−1, 19) and 152 (60).

**5.3.20. (Minor) *cis*-isomer (23).** Found: C, 62.4; H, 7.7; N, 4.6. $C_{16}H_{23}NSe$ requires: C, 62.35; H, 7.5; N, 4.55%; $\delta$ 7.50–7.30 (m, 5H, ArH), 3.10–2.80 (m, 2H, $CH_2SePh$), 2.75 (br, 1H, NH), 2.65 (m, 1H, $H_b$), 2.15 (m, 1H, $H_a$), 2.05 (m, 1H, $H_c$) and 1.80–1.00 (m, 12H, 6×$CH_2$); *m/z* (%) 308 (M−1, 9), and 152 (85).

**5.3.21. 2-(2′-Propenyl) cyclohexanone oxime *O*-allyl ether 24.** The product (72%) was obtained as a colourless oil, bp 66–72°C/0.35 mm Hg. (Found: C, 74.5; H, 10.1; N, 7.4. $C_{12}H_{19}NO$ requires: C, 74.55; H, 9.9; N, 7.25%); $\delta$ 6.00 (m, 1H, $OCH_2CH$═$CH_2$), 5.85 (m, 1H, C*H*═$CH_2$), 5.20 (m, 2H, $OCH_2CH$═C$H_2$), 5.00 (m, 2H, C$H_2$═CH), 4.50 (m, 2H, $OCH_2$), and 2.60–1.40 (m, 11H, 6×$CH_2$ and CH); *m/z* (%) 193 ($M^+$, 2), 152(12), 122(78) and 41(100).

**5.3.22. 1-(Acetyloxy)-2-[phenylseleno)methyl]octahydro-1*H*-indole 26.** Oxime *O*-allyl ether **24** (500 mg, 2.59 mmol) was added to a stirred suspension of phenylselenyl bromide (610 mg, 2.59 mmol) in dry acetonitrile (20 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 19 h. Removal of the solvent under reduced pressure gave the crude salt which, without purification, was reduced by addition to a stirred solution of sodium borohydride (2 equiv.) in 1:1 v/v methanol–chloroform (25 mL) at room temperature. Stirring was continued for 19 h when the solvent was removed under reduced pressure. The crude amine **25** was acetylated by stirring with acetic anhydride (10 mL) at room temperature over 16 h. Work up followed by flash chromatography eluting with ether afforded the product [549 mg, 63% overall from **24**] as a colourless thick oil. (Found: C, 60.7; H, 6.85; N, 4.2. $C_{17}H_{23}NOSe$ requires: C, 60.7; H, 6.9; N, 4.15%); $\delta$ $C_6D_6$) 7.80–7.00 (m, 5H, ArH), 4.30 (m, 1H, $H_c$), 4.25 (d, 1H, *J*=9.5 Hz, CHSePh), 3.05 (m, 1H, $H_d$), 2.70 (t, 1H, *J*=10.0 Hz, CHSePh), 1.80 (m, 1H, $H_e$), 1.70 (s, 3H, COMe) and 1.65–0.70 (m, 10H, 5×$CH_2$); *m/z* (%) 337 ($M^+$, 6), 180 (49), 166 (51) and 124 (100).

**5.3.23. 2,2-Dimethyl-6-heptenal.** Prepared from the 2,2-dimethyl-6-hepten-1-ol[19] by oxidation in dichloromethane with pyridinium chlorochromate. The aldehyde (58%), was obtained as a colourless oil, bp 70–71°C/0.5 mm Hg. (Found: C, 77.0; H, 11.5. $C_9H_{16}O$ requires: C, 77.1; H, 11.5%); $\delta$ 9.45 (s, 1H, CHO), 5.8 (m, 1H, C*H*═$CH_2$), 5.0 (m, 2H, C$H_2$═CH), 2.05 (d, 2H, *J*=6.5 Hz, C$H_2$CH═$CH_2$), 1.35 and 1.5(2×m, 4H, 2×$CH_2$), 1.05 (s, 6H, 2×Me); *m/z* (%) 141 ($M^+$+1, 2), 115 (4) and 88 (100).

### 5.4. General procedure for the preparation of an *O*-benzyl oxime ether from an acetal

A solution of *O*-benzylhydroxylamine hydrochloride (2 equiv.) in water was added to a solution of an acetal (1 equiv.) in ethanol. Two drops of methyl orange (0.1 wt%) were added and the solution was acidified with aq. 2N HCl until the solution ceased to change colour. The solution was then stirred at ambient temperature for 4–7 days. The reaction was worked up by addition of brine and the product was extracted with dichloromethane (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica to afford the *O*-benzyl oxime ether.

**5.4.1. 3-(2-Cyclopent-1-yl) propanal *O*-benzyl oxime 29a.** (a) Prepared (64%) as a 1:1 mixture of *E*- and *Z*- isomers from aldehyde **28a**, *O*-benzylhydroxylamine hydrochloride and sodium acetate by the general procedure.

(b) Prepared (91%) as a 1:1 mixture of *E*- and *Z*- isomers. from acetal **27a** and *O*-benzylhydroxylamine hydrochloride according to general procedure.

The product was obtained as a colourless oil. (Found: C, 78.35; H, 8.3; N, 5.9 $C_{15}H_{19}NO$ requires C, 78.6; H, 8.3; N, 6.1%); $\delta$ 7.45 (t, 0.5H, *J*=6.0 Hz, *E*-CH═N), 7.35–7.23 (m, 5H, ArH), 6.68 (t, 0.5H, *J*=5.5 Hz, *Z*-CH═N), 5.74–5.72 (m, 1H, CH═C), 5.66–5.63 (m, 1H, CH═C), 5.10, 5.05 (s, 2H, $CH_2Ph$) and 2.67–1.35 (m, 9H); *m/z* (%) 229 ($M^+$, 3), 149 (12), 91 (100), 77 (15), 67 (20) and 41 (15).); $\nu_{max}$ (film): 3080 (ArH), 2960 (C–H), 2880 (C–H), 1640 (C═N, C═C), 1450, 1370, 1210, 1040, 910, 730, and 700 $cm^{-1}$.

**5.4.2. 3-(2-Cyclohexen-1-yl) propanal *O*-benzyl oxime 29b.** (a) Prepared (83%) as a 1:1 mixture of *E*- and *Z*-isomers from aldehyde **28b**, *O*-benzylhydroxylamine hydrochloride and sodium acetate by the general procedure.

(b) Prepared (83%) as a 1:1 mixture of *E*- and *Z*- isomers from aldehyde **27b**, *O*-benzylhydroxylamine hydrochloride and sodium acetate by the general procedure.

The product was obtained as a colourless oil. (Found: C, 78.75; H, 8.65; N, 5.65 $C_{16}H_{21}NO$ requires C, 79.95; H, 8.70; N, 5.75%); $\delta$ 7.46 (t, 0.5H, *J*=6.0 Hz, *E*-CH═N), 7.39–7.28 (m, 5H, ArH), 6.69 (t, 0.5H, *J*=5.5 Hz, *Z*-CH═N), 5.70–5.68 (m, 1H, CH═C), 5.57–5.54 (m, 1H, CH═C), 5.12, 5.06 (s, 2H, $CH_2Ph$) and 2.46–1.17 (m, 11H); *m/z* (%): 243 ($M^+$, 2), 149 (10), 91 (100), 79 (12), 65 (9) and 41(15); $\nu_{max}$ (film): 3060 (ArH), 2960 (C–H), 2890, 1655 (C═N and C═C), 1500, 1455, 1370, 1050, 1030, 920, 730, and 700 $cm^{-1}$.

**5.4.3. 3-(2-Cyclohepten-1-yl) propanal *O*-benzyl oxime 29c.** (a) Prepared (88%) as a 1:1 mixture of *E*- and *Z*-isomers from aldehyde **28c**, *O*-benzylhydroxylamine hydrochloride and sodium acetate by the general procedure.

(b) Prepared (89%) as a 1:1 mixture of *E*- and *Z*- isomers from acetal **27c** and *O*-benzylhydroxylamine hydrochloride according to the general procedure.

The product was obtained as a colourless oil. (Found: C, 79.1; H, 9.1; N, 5.3 $C_{17}H_{23}NO$ requires C, 79.35; H, 9.00; N,

5.45%); δ 7.45 (t, 0.5H, *J*=6.0 Hz, *E*-CH═N), 7.35–7.27 (m, 5H, ArH), 6.68 (t, 0.5H, *J*=5.4 Hz, *Z*- CH═N), 5.79–5.73 (m, 1H, CH═C), 5.54–5.51 (m, 1H, CH═C), 5.10, 5.05 (s, 2H, $CH_2Ph$) and 2.44–1.20 (m, 13H); *m/z* (%): 257 ($M^+$, 2), 166 (5), 149 (7), 91 (100), 77 (13), 67 (8) and 41 (10).); $\nu_{max}$ (film): 3020 (ArH), 2920 (C–H), 2840, 1640 (C═N and C═C), 1490, 1450, 1365, 1050, 110, 920, 730, and 690 $cm^{-1}$.

**5.4.4. 3-(2-Cyclohepten-1-yl) propanal *O*-benzyl oxime 29d.** (a) Prepared (84%) as a 1:1 mixture of *E*- and *Z*-isomers from aldehyde **28c**, *O*-benzylhydroxylamine hydrochloride and sodium acetate by the general procedure.

(b) Prepared (93%) as a 1:1 mixture of *E*- and *Z*- isomers from acetal **27c** and *O*-benzylhydroxylamine hydrochloride according to the general procedure.

The product was obtained as a colourless oil. (Found: C, 79.5; H, 9.1; N, 5.05 $C_{18}H_{25}NO$ requires C, 79.65; H, 9.3; N, 5.15%); δ 7.44 (t, 0.5H, *J*=6.0 Hz, *E*-CH═N), 7.37–7.27 (m, 5H, ArH), 6.67 (t, 0.5H, *J*=5.5 Hz *Z*-CH═N), 5.68 (q, 1H, *J*=9.0 Hz, CH═C), 5.21–5.13 (m, 1H, CH═C), 5.09, 5.04 (s, 2H, $CH_2Ph$) and 2.47–1.08 (m, 15H); *m/z* (%): 271 ($M^+$, 14), 180 (10), 164 (31), 149 (13), 91 (100), 77 (15), 67 (18) and 55 (10). $\nu_{max}$ (film): 2920 (C–H), 2850, 1640 (C═N and C═C), 1490, 1450, 1370, 1040, 910, 740, and 700 $cm^{-1}$.

**5.4.5. 1-(7-Phenylselenyl-octahydro-[1]pyrindin-1-yl)-ethanone 33a.** *O*-Benzyl oxime ether **29a** (0.1 g, 0.43 mmol) was added to a stirred suspension of phenylselenyl bromide (0.103 g, 0.43 mmol) in dry acetonitrile (5 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 24 h. Removal of the solvent under reduced pressure gave the crude salt which, without purification, was reduced by addition to a stirred solution of sodium borohydride (0.034 g, 0.86 mmol) in 1:1 v/v methanol–dichloromethane (6 mL) at room temperature. Stirring was continued for 1 h then the solvent was removed under reduced pressure, and the amine acetylated by stirring with acetic anhydride (3 mL) at room temperature for 3 h. Work up followed by flash chromatography eluting with ether gave the product (0.055 g, 39%) which crystallised from diethylether–petroleum ether as a colourless needles, mp 123–124°C. (Found: C, 59.55; H, 6.5; N, 4.25. $C_{16}H_{21}NOSe$ requires: C, 59.6; H, 6.55; N, 4.35%); δ $C_6D_6$) (1:1 rotamer mixture) 7.76–7.48 (m, 2H, ArH), 7.12–7.0 (m, 3H, ArH), 5.30 (br, dd, 0.5H, *J*=6.5, 10.5 Hz), 4.75 (br, dd, 0.5H, *J*=1.5, 12.5 Hz), 3.83(br, dd, 0.5H, *J*=6.0, 10.5 Hz), 3.45 (q, 1H, *J*=10.0 Hz), 2.91–2.85 (m, 0.5H) and 2.43–0.60 (m, 13H, Me and cycloalky), *m/z* (%) 323 ($M^+$, 3), 166 (100), 124 (47), 107 (25), 96 (39), 79 (13), 77 (12), 43 (28) and 41(16).

**5.4.6. 1-(8-Phenylselenyl-octahydroquinolin-1-yl)-ethanone 33b.** *O*-Benzyl oxime ether **29b** (0.071 g, 0.29 mmol) was added to a stirred suspension of phenylselenyl bromide (0.070 g, 0.29 mmol) in dry acetonitrile (5 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 24 h. Removal of the solvent under reduced pressure gave the crude salt which, without purification, was reduced over 1 h by addition to a stirred solution of sodium borohydride (0.022 g, 0.58 mmol) in 1:1 v/v methanol–dichloromethane (6 mL) at room temperature. Removal of the solvent under reduced pressure followed by extraction with dichloromethane gave the crude amine **32b**, which was acetylated by stirring with acetic anhydride (3 mL) at room temperature for 3 h. Work up followed by flash chromatography eluting with ether gave the product (0.037 g, 40%) as a colourless thick oil. (Found: C, 60.7, H, 7.05; N, 3.95. $C_{17}H_{23}NOSe$ requires: C, 60.55; H, 6.8, N; 4.15%); δ (400 MHz) ($C_6D_6$) (2:1 rotamer mixture). 7.74–7.58 (m, 2H, ArH), 7.06–6.99 (m, 3H, ArH), 5.06 (br, dd, 0.5H, *J*=4.5, 12.0 Hz), 4.69 (br, d, 0.5H, *J*=13.0 Hz), 3.50(br, d, 0.5H, *J*=11.5 Hz), 3.36 (dt, 0.5H, *J*=3.5, 12.0 Hz), 3.0 (br d, 0.5H, *J*=15.0 Hz), 2.59 (dt, 0.5H, *J*=2.5, 13.5 Hz), 2.14, 1.84 (s, 3H, Me), 2.06–1.99 (m, 1H, cycloalky) and 1.68–0.86(m, 11H, cycloalky); *m/z* (%) 337 ($M^+$, 2), 180 (100), 157 (7), 138 (55), 121 (24), 96 (29), 79 (13), 77 (12), 67 (10), 43 (28) and 41(14).

**5.4.7. 5-(9-Phenylselenyl-decahydro-cyclohepta[*b*]pyrindin-1-yl)-ethanone 33c.** *O*-Benzyl oxime ether **29c** (0.065 g, 0.25 mmol) was added to a stirred suspension of phenylselenyl bromide (0.060 g, 0.25 mmol) in dry acetonitrile (5 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 24 h. Removal of the solvent under reduced pressure gave the crude salt which, without purification, was reduced over 1 h by addition to a stirred solution of sodium borohydride (0.019 g, 0.55 mmol) in 1:1 v/v methanol–dichloromethane (6 mL) at room temperature. Removal of the solvent under reduced pressure followed by extraction with dichloromethane gave the crude amine **32b**, which was acetylated by stirring with acetic anhydride (3 mL) at room temperature for 3 h. Work up followed by flash chromatography eluting with ether to gave the product (0.028 g, 32%) as a colourless thick oil. (Found: C, 61.9; H, 7.1; N, 4.1. $C_{18}H_{25}NOSe$ requires: C, 61.6; H, 7.1; N, 4.0%); δ ($C_6D_6$) (2:1 rotamer mixture) 7.53–7.29 (m, 2H, ArH), 6.96–6.90 (m, 3H, ArH), 5.17 (br, dd, 0.5H, *J*=5.5, 10.5 Hz), 4.85(br, dd, 0.5H, *J*=1.0, 13.0 Hz), 3.60 (br, dd, 0.5H, *J*=4.5, 10.0 Hz), 3.39 (dt, 0.5H, *J*=2.0, 10.5 Hz), 3.10–3.05 (m, 0.5H), 2.92 (dt, 0.5H, *J*=2.0, 13.0 Hz), 2.09–0.63 (m, 17H, Me and cycloalky); *m/z* (%) 351 ($M^+$, 2), 194 (100), 152 (46), 138 (13), 96 (28), 77 (11), 67 (12), 43(33) and 41 (16).

**5.4.8. 8-Phenylselenyl-octahydroquinoline-1-carboxylic acid *tert*-butyl ester 33e.** *O*-Benzyl oxime ether **29c** (0.122 g, 0.50 mmol) was added to a stirred suspension of phenylselenyl bromide (0.119 g, 0.50 mmol) in dry acetonitrile (5 mL) at room temperature under a nitrogen atmosphere and stirring was continued for 12 h. Additional phenylselenyl bromide (0.012 g, 0.05 mmol) was then added and stirring continued for a further 24 h. Removal of the solvent under reduced pressure gave the crude salt which, without purification, was reduced over 2 h by addition to a stirred solution of sodium borohydride (0.040 g, 1.05 mmol) in 1:1 v/v methanol–dichloromethane (8 mL) at room temperature. After removal of the solvent under reduced pressure, the residual amine was dissolved in chloroform (10 mL) and di-*tert* butyldicarbonate (0.123 g, 0.56 mmol) and triethylamine (0.075 mL, 0.55 mmol) added to the stirred solution and stirring continued at ambient temperature for 20 h. The solution was then

concentrated under reduced pressure and the residue subjected to flash chromatography on silica eluting with 1:9 v/v diethyl ether–hexane to give the product (0.063 g, 32%) which crystallised from diethylether–petroleum ether as colourless needles, mp 112–113°C. (Found: C, 61.1; H, 7.15; N, 3.5. $C_{20}H_{29}NO_2Se$ requires: C, 60.8; H, 7.35; N, 3.55%); $\delta$ (2:1 rotamer mixture). 7.58–7.51 (m, 2H, ArH), 7.32–7.18 (m, 3H, ArH), 4.31 (br, 0.5H), 4.08 (br, 0.5H), 3.88 (br, 0.5H), 3.62 (br, 0.5H) and 2.67–1.0 (m, 22H, 3×Me and cycloalky), *m/z* (%) 395 ($M^+$, 1), 295 (6), 182 (87), 157 (20), 138 (30), 109 (15), 96 (77), 77 (31), 67 (17), 57 (100) and 41 (67).

**5.4.9. 5-Methylenecyclopentyl ethanal oxime *O*-benzylether 35a.** A solution of aldehyde **34a** (0.6 g, 4.83 mmol) in acetonitrile (50 mL) was added to a solution of *O*-benzylhydroxylamine hydrochloride (0.85 g, 5.31 mmol) and sodium acetate (0.476 g, 5.8 mmol) in water (25 mL). The resulting solution was stirred at ambient temperature for 8 h and then extracted with chloroform (2×50 mL). The combined organic layer was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was subjected to column chromatography on silica eluting with 3:1 v/v petroleum ether–ether. The product (1.94 g, 91%) was obtained as a colourless thick oil, which comprised a 2:1 mixture of *E*- and *Z*- isomers. (Found: C, 77.6; H, 8.75; N, 5.6 $C_{15}H_{19}NO{\cdot}0.25H_2O$ requires C, 77.1; H, 8.35; N, 6.0%); $\delta$ 7.45 (t, 0.5H, $J$=6.5 Hz, *E*-CH=N), 7.36–7.25 (m, 5H, Ar-H, isomers), 6.70 (t, 0.5H, $J$=5.5 Hz, *Z*-CH=N), 5.11–5.05 (m, 2H, $OCH_2$), 4.82 (brs, 1H, vinyl-H, isomers), 4.75 (br s, 1H, vinyl-H, isomers) and 2.7–1.2 (m, 9H); *m/z* (%) 229 ($M^+$, 1), 91 (100), 77 (13), 65 (10) and 51 (8).

**5.4.10. 6a-[(Phenylseleno)methyl]octahydrocyclopenta[*b*]-pyrrole 38a.** Phenylselenyl bromide (0.1256 g, 0.548 mmol) was added to a solution of oxime ether **35a** (0.154 g, 0.65 mmol) in dry acetonitrile (10 mL). The resulting solution was stirred at room temperature for 16 h. Acetonitrile was removed under reduced pressure and the residue was taken up in DCM–MeOH (1:1 v/v) (10 mL), $NaBH_4$ (0.041 g, 1.09 mmol) added and the mixture stirred at room temperature for 1 h. The solvent was then evaporated under reduced pressure and the residue subjected to column chromatography on slica, eluting with 100:10:1 v/v/v DCM–MeOH–$NH_3$ (35% w/w ammonia solution). The product **38a** (0.094 g, 61%) was obtained as pale yellow thick oil. (Found: C, 57.75; H, 6.85; N, 4.8 $C_{14}H_{19}NSe{\cdot}0.5H_2O$ requires: C, 57.9; H, 6.9; N, 4.8%). HRMS: 280.0568, $C_{14}H_{19}NSe$ requires: 280.0560; $\delta$ 7.51–7.20 (m, 5H, Ar-H), 6.84 (t, 1H, $J$=2.5 Hz, NH), 3.66 (d, 1H, $J$=7.5 Hz, $H_{b1}$), 3.24 (d, 1H, $J$=13.0 Hz, $H_{b2}$), 2.95 (m, 1H, $H_d$), 2.60 (m, 1H, $H_{c1}$), 2.35 (m, 1H, $H_{c2}$) and 2.12–1.41 (m, 8H); *m/z* (%) 279 ($M^+$, 7), 198 (43), 138 (100), 91 (39), 77 (54), 67 (30) and 41(40).

**5.4.11. 2-Methylenecyclohexyl ethanal oxime *O*-benzylether 35b.** A solution of aldehyde **34b** (1 g, 7.24 mmol) in acetonitrile (100 mL) was added to a solution of *O*-benzylhydroxylamine hydrochloride (1.272 g, 7.97 mmol) and sodium acetate (0.713 g, 8.69 mmol) in water (50 mL). The resulting solution was stirred at ambient temperature for 8 h and then extracted with chloroform (2×150 mL). The combined organic layer was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was subjected to column chromatography on silica eluting with 3:1 v/v petroleum ether–ether. The product (1.51 g, 86%) was obtained as a colourless thick oil, which comprised a 2:1 mixture of *E*- and *Z*- isomers. (Found: C, 78.75; H, 8.9; N, 5.65 $C_{16}H_{21}NO$ requires C, 78, 95; H, 8.7; N, 5.75%). $\delta$ 7.46 (t, $J$=6.0 Hz, *E*-CH=N), 7.39–7.19 (m, 5H, Ar-H, isomers), 6.65 (t, $J$=5.0 Hz, *Z*-CH=N), 5.10–5.01 (m, 2H, $OCH_2$), 4.67 (brs, 1H, vinyl-H, isomers), 4.53 (brs, 1H, vinyl-H, isomers) and 2.59–0.87 (m, 11H); *m/z* (%) 243 ($M^+$, 1), 152 (10), 121 (19), 91(100), 77 (15), 67 (17), 55 (10) and 41(15).

**5.4.12. 7a-[(Phenylseleno)methyl]octahydro-1*H*-indole 38b.** Phenylselenyl bromide (1.16 g, 4.93 mmol) was added to a solution of oxime ether **35b** (1 g, 4.11 mmol) in dry acetonitrile (100 mL). The resulting solution was stirred at room temperature for 16 h. Acetonitrile was removed under reduced pressure and the residue was taken up in DCM–MeOH (1:1 v/v) (100 mL), $NaBH_4$ (0.311 g, 8.23 mmol) added and the mixture stirred at room temperature for 1 h. The solvent was then evaporated under reduced pressure and the residue subjected to column chromatography on silica eluting with 1:1 v/v petroleum ether–ether. The product (0.8 g, 67%) was obtained as pale yellow thick oil. (Found: C, 57.6; H, 6.95; N, 4.5 $C_{15}H_{21}NSe{\cdot}H_2O$ requires: C, 57.7; H, 7.1; N, 4.5%). $\delta$ ($C_6D_6$) 7.55–6.94 (m, 5H, Ar-H), 6.52–6.51 (brs, 1H, NH), 3.51 (d, 1H, $J$=7.6 Hz, $H_{b1}$), 3.10 (d, 1H, $J$=8 Hz, $H_{b2}$), 2.35 (m, 1H, $H_d$), 1.95 (m, 1H, $H_{c1}$), 1.66 (m, 1H, $H_{c2}$) and 1.89–0.92 (m, 10H); *m/z* (%) 295 ($M^+$, 6), 212(18), 198(57), 140(100), 124(78), 95(31), 77(21) and 67(29).

**5.4.13. Non-8-en-4-one oxime *O*-benzylether 41.** Prepared by the general procedure from non-8-en-4-one. The product (1.47 g, 83%) was obtained as a colourless oil. (Found: C, 78.2; H, 9.2; N, 5.9, $C_{16}H_{23}NO$ requires C, 78.4; H, 9.4; N, 5.7%); $\delta$ 7.35–7.2 5 (m, 5H, Ar-H), 5.80–5.75 (m, 1H, CH=), 5.06 (s, 2H, $CH_2$-Ar), 5.04–4.94 (m, 2H, $CH_2$=), 2.34–2.27 (m, 2H, C$H_2$CH=C), 2.18–2.03 (4H, 2×C$H_2$–CH=N), 1.61–1.48 (m, 4H, 2×CH2) and 0.91 (q, 3H, $J$=7.2 Hz, Me); *m/z* (%): 245 ($M^+$, 1), 202(4), 111(12), 91(100), 77 (8) and 41 (16);. $\nu_{max}$ (film): 2910 (C–H), 2860 (C–H), 1630 (C=N, C=C) and 1450 ($CH_2$=) $cm^{-1}$.

**5.4.14. *cis*-2-Phenylselenylmethyl-6-propyl piperidine 44.** Prepared by the general procedure from non-8-en-4-one oxime *O*-benzyl ether **41** The product (0.47 g, 78%) was obtained as a pale yellow oil. (Found: C, 60.9; H, 7.8; N, 4.7. $C_{15}H_{23}NSe$ requires C, 60.65; H, 7.75; N, 4.75%); $\delta$ (400 MHz) ($C_6D_6$) 7.51–7.48 (m, 2H, Ar-H), 7.00–6.92 (m, 3H, Ar-H), 2.92 (dd, 1H, $J$=4.5, 12.0 Hz, $H_a$), 2.75 (dd, 1H, $J$=8.5, 12.0 Hz, $H_b$), 2.56 (m, 1H, $H_c$), 2.33 (m, 1H, $H_d$), 2.10 (br, 1H, NH), 1.64–0.93 (m, 10H, 5×$CH_2$) and 0.85 (t, 3H, $J$=7.0 Hz, Me); *m/z* (%): 298 (M−1, 3), 24 5(5), 126 (100), 96 (18), 82 (14), 77 (12), 55 (17), 43 (11) and 41 (20); $\nu_{max}$ (film): 3060 (ArH), 2905 (C–H), 2880 (C–H), 1560 (N–H) and 1430 ($CH_3$) $cm^{-1}$.

### 5.5. n.O.e data

Irradiation of the signal for proton $H_c$ ($\delta$ 2.56) caused a 4%

enhancement of the signal for proton $H_d$ ($\delta$ 2.32) and conversely irradiation of the signal for proton $H_d$ caused a 7% enhancement of the signal for proton $H_c$.

**5.5.1. Dihydropinidine hydrochloride 45.** Tributyltin hydride (0.18 mL, 0.67 mmol) and AIBN (0.007 g, 0.04 mmol) were added to a stirred solution of piperidine **44** (0.102 g, 0.34 mmol) in dry THF (10 mL) under a nitrogen atmosphere. The solution was stirred and boiled under reflux for 5 h, cooled and HCl gas bubbled through the solution for 5 min. The solution was then concentrated under reduced pressure and diethylether (10 mL) added to the residue to precipitate the hydrochloride salt which, after filtration, afforded dihydropinidine hydrochloride **45** (0.044 g, 72%) as a colourless amorphous solid, mp 209–211°C (lit. mp 207–211°C).[11] The spectral properties were identical with the literature data[11] $\delta$ 9.40 (br, 1H, NH), 9.10 (br, 1H, NH), 3.10–3.07 (m, 1H, CH-N), 2.94–2.88 (m, 1H, CH-N), 2.16–1.25 (m, 13H, Me and 5×$CH_2$) and 0.91 (t, 3H, $J$=7.5 Hz, Me); $m/z$ (%): 177 ($M^+$, 1), 140 (5), 126 (12), 98 (100), 70 (18), 55 (17), 44 (18) and 41 (19).

### 5.6. Single crystal X-ray diffraction analyses of 33a and 33e

Crystallographic data for both structures were measured on a Stoe STADI4 4-circle diffractometer $\omega-\theta$ scans and Mo Kα radiation for **33e** ($\lambda$=0.71073 Å) and Cu Kα radiation for **33a** ($\lambda$=1.54184 Å). Both structures were solved by direct methods using SHELXS-86[22] and refined by full-matrix least-squares (based on $F^2$) using SHELXL-93.[23] The weighting scheme used $w=[(2(F_o^2)+(xP)^2+yP]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. Refinement was the same for both structures in that all non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals $wR_2$ and $R_1$, given below, are defined as $wR_2=(\sum[w(F_o-F_c^2)^2]/\sum[wF_o^4])^{1/2}$ and $R_1=\sum||F_o|-|F_c||/\sum|F_c|$.

**5.6.1. Crystal data for 33a.** $C_{16}H_{21}NOSe$, 0.53×0.29×0.17 $mm^3$, $M$=322.30, orthorhombic, space group $P2_12_12_1$, $a$=9.9109(3), $b$=10.6114(3), $c$=13.6646(4) Å, $V$=1437.09(8) $Å^3$, $Z$=4, $D_c$=1.49 mg $m^{-3}$, $\mu$=3.46 $mm^{-1}$, $F$(000)=664, $T$=200 K. Data collection: $5.28<\theta<64.38°$; 2283. Unique data collected of which 2268 with $F_o>4.0\ \sigma(F_o)$ were considered 'observed'. Structure refinement: number of parameters=174, goodness of fit, $s$=1.103; $wR_2$ (all data)=0.0717, $R_1$ (observed data)=0.0274.

**5.6.2. Crystal data for 33e.** $C_{20}H_{29}NO_2Se$, 0.75×0.53×0.39 $mm^3$, $M$=394.40, orthorhombic, space group $Pbca$, $a$=10.8555(13), $b$=16.9360(11), $c$=21.6580(13) Å, $V$=3981.8(6) $Å^3$, $Z$=8, $D_c$=1.32 mg $m^{-3}$, $\mu$=1.897 $mm^{-1}$, $F$(000)=1648, $T$=293 K. Data collection: $1.88<\theta<24.99°$; 3501 unique data collected of which 1966 with $F_o>4.0\ \sigma(F_o)$ were considered observed. Structure refinement: number of parameters=220, goodness of fit, $s$=1.250; $wR_2$ (all data)=0.1441, $R_1$ (observed data)=0.0644.

Supplementary data-sets for both structures, which include hydrogen co-ordinates, all thermal parameters and complete sets of bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre (**33a**: CCDC 167389; **33e**: CCDC 167390) and are available on request.

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