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Selenocyclisations of homoallylic sulfonamides: stereoselective methods for the elaboration of substituted pyrrolidines, pyrrolines and derivatives

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Abstract—Selenocyclisations of the homoallylic sulfonamides [e.g., **26**, **28** and **30**] using phenylselanyl halides lead exclusively to β-selanyl-pyrrolidines [e.g., **27**, **29** and **31**] by an overall 5-*endo-trig* pathway, but with considerable variations in the stereochemical outcome, depending upon the substituents and the precise conditions used. Subsequent oxidative eliminations lead smoothly to the corresponding 3-pyrrolines and thence to poly-hydroxylated pyrrolidines.

1. Introduction

The introduction of a phenylselanyl group into a molecule can serve a number of synthetic purposes, although, most often, subsequent oxidation to the corresponding selenoxide and thermal [2,3]-elimination involving a proton β-to the heteroatom leading to alkene formation is its immediate fate.[1,2] Less often, a phenylselanyl group can serve as a radical precursor or assist in the stabilisation of a carbanion. There are a number of methods available for the introduction of selanyl groups, many of which have been applied to the synthesis of selanyl-pyrrolidines **1**, perhaps the simplest being the direct addition of a selanyl halide to a 2,5-dihydropyrrole, the resulting β-halo selanides **2** being useful as synthetic intermediates for subsequent ring formation, amongst other applications (Fig. 1).[3]

Similar additions to 2,3-dihydropyrroles in the presence of amines or inorganic azides result in synthetically useful α-amino-[4] and α-azido-selanides **3**, respectively, as a result of interception of the presumed cyclic phenylselanonium ion by the nitrogen nucleophile, probably directed by the ring nitrogen (Fig. 1).[5]

A much more common strategy for the introduction of a phenylselanyl group into such *N*-heterocycles is the trapping of an enolate derived from a five-membered lactam [cf. **4**] or pyrrolidine carboxylate, with a phenylselanyl halide.[6] Such an addition is most commonly followed by oxidative elimination,[7] a reaction which can sometimes pose unexpected problems[8] but which thereby leads to an α,β-unsaturated carbonyl system primed, amongst other transformations, for Michael additions. Rather than elimination, such phenylselanyl groups [cf. **5**] can also serve as precursors to carbon-centred radicals **6**.[9] Another very common strategy for the introduction of a phenylselanyl group into a pyrrolidine is by S_N2 attack of a selenium nucleophile on an activated β-hydroxy-pyrrolidine **7** leading to derivatives **8** (Fig. 1).[10] A somewhat less common but elegant procedure for the formation of β-selanyl-pyrroles involves [1,3]-dipolar cycloadditions between azomethine ylides and phenylselanylethene [phenyl(vinyl)selane].[11]

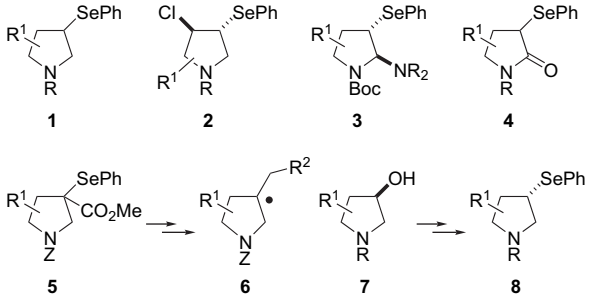

Figure 1. Various types of β-selanyl-pyrrolidines.

Inevitably perhaps, selenocyclisations have been applied to the elaboration of selanyl-pyrrolidines. In early examples,[12] an electrophilic selenium species generated from diphenyl diselenide using ammonium persulfate (peroxydisulfate)

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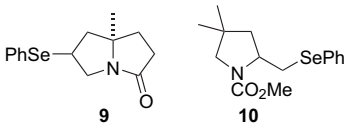


Figure 2. Pyrrolidines from 5-*endo* and 5-*exo* selenocyclisations.

was used to induce a 5-*endo-trig* cyclisation leading to the pyrrolizidinone **9** from the corresponding γ-allyl lactam. Prior to this, Clive had shown that 5-*exo* selanyl-cyclisations of *N*-alkenyl carbamates were viable and gave good yields of the pyrrolidines **10** (Fig. 2).[13]

Using more conventional conditions (phenylselanyl halides and a mild base, Na_2CO_3), it was subsequently found that homoallylic benzylamines **11** underwent both 4-*exo* and 5-*endo* cyclisation modes to give high yields but of mixtures of azetidines **12** and pyrrolidines **13**. The ratio of products depended strongly upon the substituents (alkyl or aryl), solvents (acetonitrile or dichloromethane) and the selanyl halide employed for the cyclisation (Cl or Br) (Fig. 3).[14] Pyrrolidines **13** were especially favoured by a combination of phenylselanyl bromide in dichloromethane, but other patterns were more difficult to discern. Related cyclisations can also be carried out asymmetrically: the 5-*endo* mode seems effective only in examples having a distal phenyl group [**14** and **16**] but with such precursors, diastereoisomer ratios in excess of 9:1 can be obtained in the products [**15** and **17**, respectively] using an enantiopure arylselanyl triflate [Ar*SeOTf].[15]

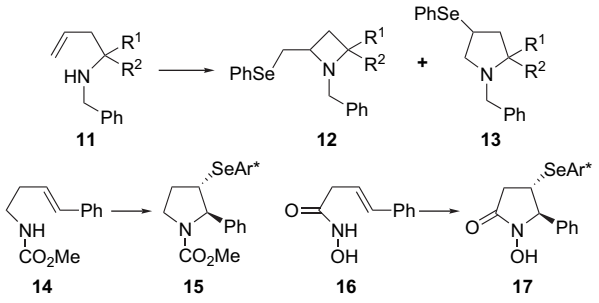
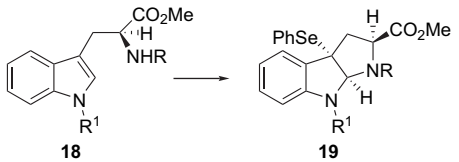


Figure 3. Pyrrolidines from 5-*endo* selenocyclisations.

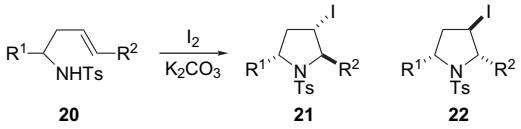
Imine analogues corresponding to the benzylamines **11** also undergo similar selenocyclisations to give exclusively β-selanyl-pyrrolidines, following borohydride reduction of the resulting iminium species, but with little stereoselectivity.[16] Related cyclisations are also known, which give five-membered ring products from selenocyclisations of *O*-allylic hydroxamic acids, hydroxylamines and hydrazines.[17]

A final and rather spectacular example involves 5-*endo-trig* cyclisation of tryptophan derivatives **18** to give the benzopyrrolizidines **19**, serving both to block the usual chemistry of the indole residue as well as providing other opportunities for further functionalisation (Scheme 1).[18]



Scheme 1. Benzopyrrolizidines from 5-*endo* selenocyclisations of tryptophanes.

It was against this background that we wondered if related 5-*endo-trig* selenocyclisations of *N*-tosylsulfonyl homoallylic amines **20** might provide a useful approach to β-selanyl-pyrrolidines and especially if it would be possible to control both the regiochemistry and the stereoselectivity of such projected cyclisations. This was far from certain, in view of the foregoing observations of the lack of regiocontrol in selenium-induced cyclisations of the allylic benzylamines **11**[14] and of the very limited success of related cyclisations when applied to homoallylic carbamates (Fig. 3). Further, our own studies on related iodocyclisations of the sulfonamides **20** had revealed sensitivity to isomerisation under acidic conditions. Thus, while exposure of sulfonamides **20** to iodine in the presence of potassium carbonate led very largely to the 2,5-*trans* isomers **21**, in the absence of base, the corresponding 2,5-*cis* isomers **22** were obtained, usually exclusively (Scheme 2).[19] Additional experiments pointed to an acid-catalysed ring opening and re-closure towards the more thermodynamically stable *cis* isomers **22** as being responsible. It was therefore quite uncertain at the outset how such substrates would respond to selenocyclisation.



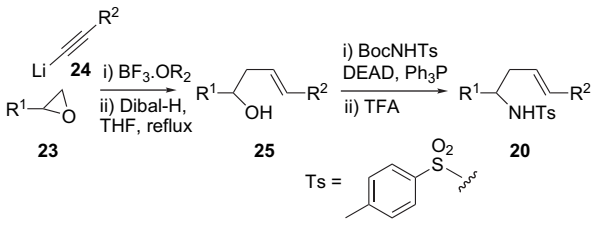
Scheme 2. 5-*endo* Iodocyclisations of homoallylic sulfonamides.

A further motivation of our investigations of such a selenium-mediated process was the finding that elimination of the elements of hydrogen iodide from the iodo-pyrrolidines **21** or **22** failed to give acceptable yields of the anticipated pyrrolines; we expected that the corresponding selanyl-pyrrolidines would be much more amenable to such eliminations, given that their formation could be controlled. The general principle of overall 5-*endo-trig* electrophile-driven cyclisation is now well established as a useful and often highly stereoselective method for the synthesis of five-membered saturated heterocycles.[20] An additional attraction of this type of heterocyclic synthesis is that ring formation is accompanied by the incorporation of a potentially useful functional group. Herein, we report in full on our initial studies of such cyclisations.[21]

2. Results and discussion

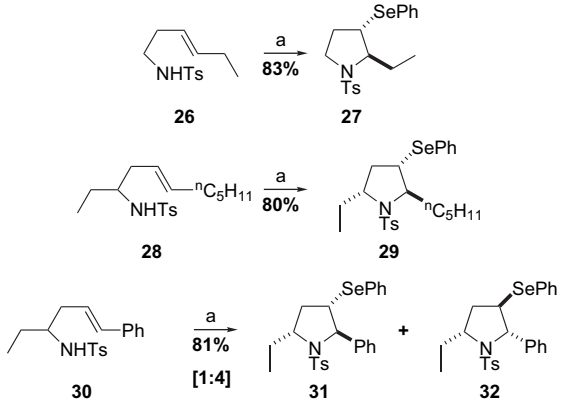
We first chose to examine the prospects for 5-*endo-trig* selenocyclisations of both alkyl and aryl substituted homoallylic sulfonamides **20**. These were all synthesised[19] by the addition of an acetylide **24** to a monosubstituted epoxide **23** in the presence of boron trifluoride etherate[22] or, better, the corresponding tetrahydrofuran complex,[23] followed by reduction using either lithium aluminium hydride or Dibal-H in hot tetrahydrofuran (Scheme 3). The necessary sulfonamide group was then introduced into the resulting homoallylic alcohols **25** by Mitsunobu reaction with *N*-Boc tosylamide [BocNHTs], a procedure introduced by the Weinreb group.[24] Deprotection using trifluoroacetic acid completed the sequence.

Guided by the early results of Clive,[13] we were delighted to find that the simplest substrate **26** was converted smoothly



Scheme 3. Precursor synthesis.

into a single pyrrolidine, assumed to be the 2,3-*trans* diastereoisomer **27** (see below), in excellent yield by brief exposure to phenylselanyl chloride in dichloromethane at low temperature (−78 °C) (Scheme 4). Similarly, the more highly substituted precursor **28** gave essentially a single product **29** under the same conditions, contaminated with what appeared to be traces of other pyrrolidine diastereoisomers, according to ^{1}H NMR spectroscopy.

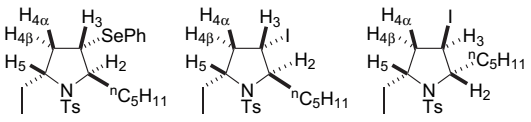


Scheme 4. Reagents and conditions: PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C, <1 h.

Unfortunately, under the same relatively straightforward conditions, the related styryl derivative **30** gave a mixture of the trisubstituted pyrrolidines **31** and **32**, but still in good yield. In contrast to similar cyclisations of the homoallylic benzylamines **11** (Fig. 3), we did not detect any azetidine formation.

The stereochemistries of the present [**27**, **29**, **31** and **32**] and subsequent β-selenopyrrolidines were determined principally by comparisons between their proton coupling constants and those displayed by the corresponding β-iodopyrrolidines. Structural assignments in the latter cases have been firmly established by both NOE experiments and X-ray crystallographic analysis.[19] An exception was the very first example (**27**), in which overlapping resonances prevented such comparisons, although these data did allow a definite assignment of a pyrrolidine rather than an azetidine structure to this product. Hence, the *trans*-stereochemistry is based largely on the assumption of trans addition of the amine and selenium groups across the alkene, for which there seems to be few if any exceptions and certainly none in the present reactions. The other comparative *J* values are set out in Figure 4.

Similar comparisons between the 2-phenyl-3-seleno and 2-phenyl-3-iodo-pyrrolidines [**31**, **32** and **35**, **36**, respectively]



	29	**33**	**34**
$J_{2,3}$	1.4	1.7	3.4
$J_{3,4\alpha}$	7.5	6.6	5.7
$J_{3,4\beta}$	1.9	2.2	3.5
$J_{4\alpha,5}$	8.7	8.8	7.5
$J_{4\beta,5}$	3.3	3.2	6.8
$J_{2,1'\text{-}CH_2}$	10.1, 2.9	10.3, 3.3	9.1, 3.6
$J_{5,1'\text{-}CH_2}$	11.3, 3.3	11.3, 3.1	8.0, 4.2

Figure 4. Comparative coupling constants in hertz for β-seleno- and β-iodo-pyrrolidines.

gave much the same support for the stereochemical assignments (Fig. 5).

These data are also consistent with those shown in Figure 4, and hence it appeared that such stereochemical assignments were on a sound basis. Further, these were also in accord with a likely initial chair-like transition state conformation **37** controlled by an equatorial positioning of the substituents 'R' attached to the sp^3 carbon (Fig. 6).

Consonant with these assignments and with the conformation **37** were the outcomes of similar selenocyclisations of the more substituted homoallylic sulfonamides **38** and **40**.[19] Each proceeded smoothly under the same conditions to give only the diastereoisomers **39** and **41**, respectively (Scheme 5).

	31 R = SePh	**35** R = I	**32** R = SePh	**36** R = I
$J_{2,3}$	2.1	2.3	5.9	4.9
$J_{3,4\alpha}$	7.6	8.7	7.6	6.2
$J_{3,4\beta}$	2.5	2.4	5.6	6.2
$J_{4\alpha,5}$	6.4	6.7	4.8	6.2
$J_{4\beta,5}$	2.5	3.0	5.2	6.2

Figure 5. Comparative coupling constants in hertz for 2-phenyl-pyrrolidines.

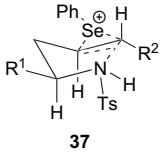
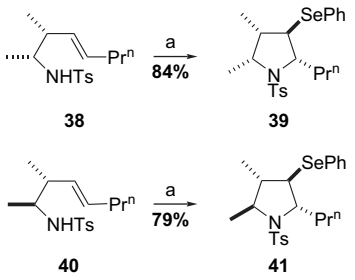


Figure 6. Possible chair-like conformation leading to the initial 2,5-*trans*-pyrrolidines.



Scheme 5. Reagents and conditions: PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C, <1 h.

Once again, initial structural assignments were made on the basis of comparisons between these products and the corresponding iodo-pyrrolidines **42** and **43**, respectively (Fig. 7).[19]

The close correspondence between the two pairs of coupling constants strongly supports these assignments, as do the likely transition state conformations, which are extrapolations of the simpler proposal **37** (Fig. 6). In the first example where the product **39** has the selanyl group positioned trans to the other three substituents, one of the methyl substituents must be positioned axially, given the intermediacy of such a chair-like conformation. The preference is therefore clearly in favour of that conformation **44** in which the methyl group adjacent to the selenonium ion is placed in an equatorial position (Fig. 8). By contrast, the conformation **45** leading to the 'all-trans' product **41** has all substituents positioned equatorially, thereby removing any realistic element of choice regarding other possible conformations. These two assignments were also supported by subsequent elimination reactions described in Figure 8.

We then returned to the problem of the non-stereoselective cyclisation of the phenyl derivative **30** (Scheme 4). On the assumption that this might be due to acid-catalysed isomerisation of some kind, most probably by ring opening and

	39 R = SePh	42 R = I	41 R = SePh	43 R = I
$J_{2,3}$	8.3	8.7	5.3	6.3
$J_{3,4}$	11.4	11.6	8.7	9.2
$J_{4,5}$	7.2	7.2	8.3	9.4
$J_{2,1'\text{-}CH_2}$	4.6, 5.1	3.6, 6.2	4.2, 7.6	7.6, 4.1

Figure 7. Comparative coupling constants for 4,5-dimethylpyrrolidines.

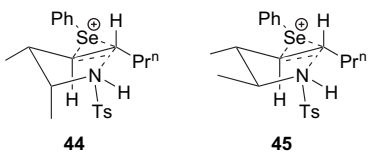
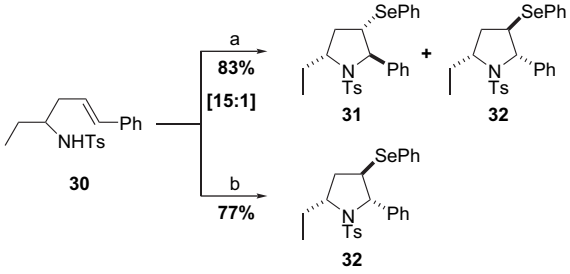


Figure 8. Possible chair-like conformations leading to 4,5-dimethylpyrrolidines **39** and **41**.

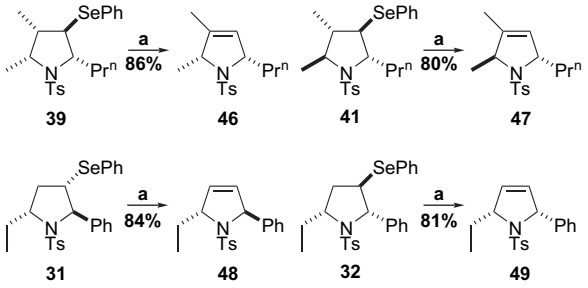
re-closure as in the case of the related iodo-pyrrolidines (Scheme 2),[19] we felt that the generation of free hydrogen chloride during the cyclisation might be responsible. The cyclisation was therefore repeated but in the presence of an equivalent of anhydrous potassium carbonate (Scheme 6). This resulted in a distinct increase in the proportion of the 2,5-*trans* isomer **31** formed, lending weight to our supposition that acid-catalysed isomerisation was taking place.



Scheme 6. Reagents and conditions: (a) PhSeCl (1.1 equiv), K_2CO_3 (1 equiv), water (trace), CH_2Cl_2, −78 °C, < 1 h; (b) **30** (0.14 mmol), PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C then add 10 M HCl (one drop), 0.5 h.

The best result was obtained when a small amount of water was also added, presumably to facilitate reaction between the base and the acid generated as the cyclisation proceeded. This 15:1 ratio in favour of the 2,5-*trans* isomer **31** then suggested that if additional acid were to be added, then isomerisation ought to be encouraged. This turned out to be the case: when a drop of concentrated hydrochloric acid was added at the outset, only the 2,5-*cis* isomer **32** was isolated, confirming our supposition that this is the thermodynamic isomer, formed via the initial kinetic product **31**.

To both show one synthetic utility of these selanyl-pyrrolidines and also to provide further evidence for the assigned stereochemistries, we next examined the viability of oxidative elimination reactions. As shown in Scheme 7, these all proceeded smoothly under very simple conditions.[7,25]



Scheme 7. (a) H_2O_2 (30%), THF, 20 °C, 1 h.

In the cases of 4,5-dimethylpyrrolidines **39** and **41**, each possesses a 3,4-*trans* substitution pattern and hence the derived selenoxides **50** are perfectly set up to undergo *syn* eliminations to give the observed products **46** and **47**, respectively (Fig. 9). By contrast, the corresponding iodo-pyrrolidines **42** and **43**[19] failed to give more than traces of the 3-pyrrolines **46** and **47** under conditions (DBU, hot toluene[19,26]), which delivered good yields of this product type from iodo-pyrrolidines having no substituents in the 4-position. While the presence of the β-methyl group might contribute to this, presumably the major reason for this failure is the *syn*-disposition of the 4-proton and the 3-iodo atoms.

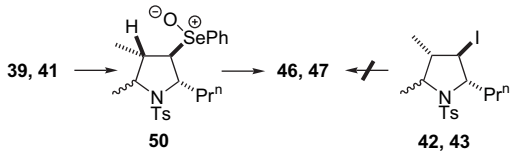
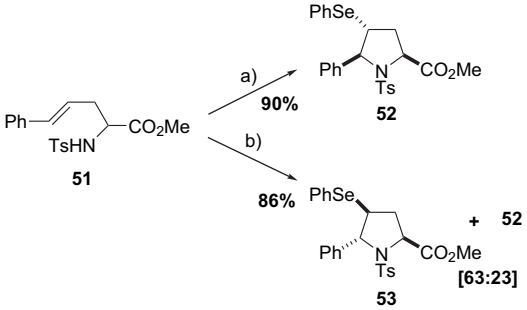


Figure 9. Eliminations from β-selanyl- and β-iodo-pyrrolidines.

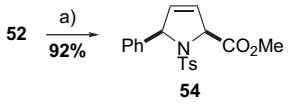
As expected, both 2-phenyl-pyrrolidines **31** and **32** underwent smooth elimination to give excellent yields of the corresponding pyrrolines **48** and **49** (Scheme 7). In both cases, no isomerisation was observed and both displayed spectroscopic and analytical data, which correlated exactly with the same products derived from the corresponding iodopyrrolidines **35** and **36** (Fig. 5).[19]

With the aim of demonstrating further the utility of this chemistry, we felt that examples with more reactive functional groups, which would subsequently be available for further manipulation, ought to be tested. In view of the foregoing results, we also chose to restrict this investigation to the seemingly more awkward aryl substituted alkenes. Hence, the cinnamyl glycinate **51** was chosen as the first test substrate; this was readily prepared from cinnamyl bromide and the enolate of *N*-benzylidene glycinate using the excellent Stork procedure,[27] followed by exchange of the protecting group.[19] When subjected to 'thermodynamic' conditions (Scheme 4), once again mixtures of the 2,5-*cis* and *trans* selanyl-pyrrolidines were obtained. Even at ambient temperature, when using phenylselanyl chloride in the absence of base, gross mixtures of diastereoisomers were obtained; for example, prolonged reaction in dichloromethane led to a 3:1 mixture but to a more useful 9:1 mixture in favour of the 2,5-*cis* isomer in acetonitrile. It was only when we used phenylselanyl bromide in dichloromethane for an extended period at ambient temperature that only the 2,5-*cis* isomer **52** was isolated (Scheme 8). Much of the same result could also be obtained using acetonitrile as solvent.



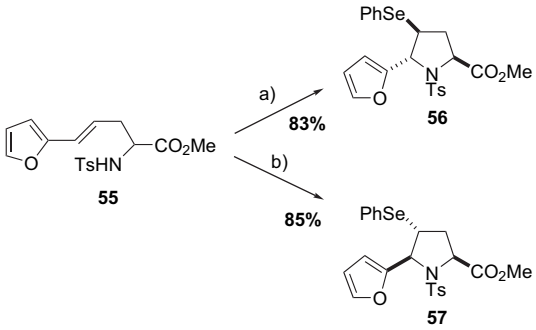
Scheme 8. (a) PhSeBr, CH_2Cl_2, 20 °C, 72 h; (b) PhSeCl, K_2CO_3, −78 to 20 °C.

Many attempts to obtain the 2,5-*trans* isomer **53** as essentially the sole product failed or were not repeatable with certainty. Two of the better results are detailed in Section 3; this particular cyclisation turned out to be the most capricious of all those studied and results, in terms of stereochemistry, were very often completely irreproducible. The relative stereochemistries of the two products **52** and **53** were again assigned on the basis of comparisons of coupling constants, both with the foregoing selanyl-pyrrolidines and with related iodo-pyrrolidines.[28] In the case of the 2,5-*cis* isomer **52**, subsequent oxidative elimination of the selenium group proceeded uneventfully to give an excellent yield of the 3-pyrroline **54** (Scheme 9).



Scheme 9. (a) H_2O_2 (30%), THF, 20 °C, 1 h.

We then turned to cyclisations of the related 2-furyl derivative **55**. In this case, we identified three additional features. Firstly, the furan residue would very likely be sensitive to the acidic conditions generated during cyclisations conducted in the absence of base. Secondly, if conditions could be found that gave single diastereoisomers, then the furan ring could subsequently be oxidatively cleaved to give the corresponding carboxylate group, thereby enabling further homologation of the initial product(s). Finally, an additional beneficial feature of the furan should be as a facilitating group for the cyclisations; our previous studies on iodocyclisations of similar substrates having 2-furyl substituents had suggested that the furyl oxygen actively participates in the cyclisations.[29] In view of the first concern, we first examined cyclisations under basic conditions and were pleased to find that exposure of the substrate **55** to phenylselanyl chloride at low temperature in tetrahydrofuran containing 1.5 equiv of potassium carbonate gave an excellent yield of the hoped-for 2,5-*trans* diastereoisomer **56**, as essentially a single product (Scheme 10). Rather surprisingly, however, when the same reaction was carried out at ambient temperature, but in acetonitrile, only the corresponding 2,5-*cis* isomer **57** was obtained, again in excellent yield. Once again, the stereochemistries were assigned on the basis of comparisons with the foregoing data.

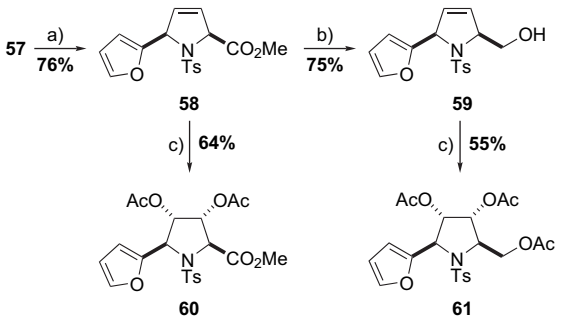


Scheme 10. (a) PhSeCl, THF, K_2CO_3 (1.5 equiv), −78 °C, 2 h; (b) PhSeCl, MeCN, K_2CO_3 (1.5 equiv), 20 °C, 2 h.

This somewhat surprising result probably reflects the anticipated participation by the furyl oxygen. Even with this effect,[29] the stereochemical outcome of the low temperature cyclisation leading to the 2,5-*trans* isomer **56** is again consistent with the intermediacy of a chair-like transition state conformation (Figs. 6 and 8). An explanation for the formation of the 2,5-*cis* isomer **57** is not so obvious, beyond it being the thermodynamically more stable isomer, which is formed at higher temperature.

We have briefly exemplified some of the synthetic potential of these selanyl-pyrrolidines using the 2,5-*cis*-2-furyl isomer **57** (Scheme 11). Oxidative elimination once again occurred

uneventfully to provide an excellent return of the expected 3-pyrroline **58**, which was subsequently smoothly reduced to the corresponding 3-pyrroline methanol **59** using Dibal-H.



Scheme 11. (a) H_2O_2 (30%), THF, 20 °C, 2 h; (b) Dibal-H, toluene, 0 °C, 3 h; (c) OsO_4 in *t*-BuOH, aqueous acetone, 20 °C, 16 h then evaporate solvents and add Ac_2O and dry pyridine, 20 °C, 20 h.

Osmylation of both pyrrolines in aqueous acetone followed by per-acetylation (to facilitate isolation) was essentially completely stereoselective and gave reasonable yields of the two fully functionalised pyrrolidines **60** and **61**, which should serve as useful precursors to a wide range of polyhydroxylated pyrrolidines and derived bicyclic systems.

In conclusion, this type of overall 5-*endo-trig* selenocyclisation has clear potential for the rapid assembly of pyrrolidines, pyrrolines and derived structures in a controlled and stereoselective manner. However, exceptions to this may occur in a few substrates having aryl substituents at the distal end of the alkene group, when stereochemistry can be more difficult to control.

3. Experimental

3.1. General

NMR spectra were recorded using a Bruker WM or DPX spectrometers, operating at 250 or 400 MHz for ^{1}H NMR spectra and at 67.5 or 100.6 MHz for ^{13}C NMR spectra, respectively. Unless stated otherwise, NMR spectra were measured using dilute solutions in deuteriochloroform. All NMR measurements were carried out at 30 °C and chemical shifts are reported as parts per million on the delta scale downfield from tetramethylsilane (TMS: δ=0.00) or relative to the resonances of $CDCl_3$ (δ=7.27 ppm in proton spectra and δ=77.0 ppm for the central line of the triplet in carbon spectra). Coupling constants (*J*) are reported in hertz. Infrared spectra were recorded as thin films for liquids and as Nujol mulls for solids, using a Perkin–Elmer 1600 series FTIR spectrophotometer and sodium chloride plates. Low-resolution mass spectra were obtained using a VG Platform II Quadrupole spectrometer operating in the electron impact (EI; 70 eV) or atmospheric pressure chemical ionisation (ApcI) modes, as stated. High-resolution mass spectrometric data were obtained from the EPSRC Mass Spectrometry Service, University College, Swansea, using the ionisation modes specified. All mass spectroscopic data involving selanides were compared against selenium-80. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were obtained using a Perkin–Elmer 240C Elemental Microanalyser.

All reactions were conducted in oven-dried apparatus under an atmosphere of dry nitrogen unless otherwise stated. All organic solutions from aqueous work-ups were dried by brief exposure to dried magnesium sulfate, followed by gravity filtration. The resulting dried solutions were evaporated using a Büchi rotary evaporator under water aspirator pressure and at ambient temperature unless otherwise stated. Column chromatography was carried out using Merck Silica Gel 60 (230–400 mesh). TLC analyses were carried out using Merck silica gel 60 F_{254} pre-coated, aluminium-backed plates, which were visualised using ultraviolet light or potassium permanganate or ammonium molybdenate sprays.

Ether refers to diethyl ether and petrol to the fraction boiling at 60–80 °C unless stated otherwise.

All starting materials were synthesised as described in full in Ref. 19.

3.2. Selenocyclisations: general procedure A

A stirred solution of the cyclisation precursor (1 mmol) in dry dichloromethane (5 ml) was cooled to −78 °C and solid phenylselanyl chloride (1.1 mmol) added portionwise. Stirring was continued at this temperature until cyclisation was complete, typically after 0.5–1 h, according to TLC analysis. The solvent was evaporated and the residue purified by column chromatography.

3.2.1. (2*RS*,3*SR*)-2-Ethyl-3-(phenylselanyl)-1-tosylpyrrolidine 27. (*E*)-Homoallylic tosylamide **26** (20 mg, 0.08 mmol) was cyclised according to general procedure A to leave an orange oil, which was purified by column chromatography (dichloromethane) to give the *title compound* **27** (30 mg, 83%) as a clear, colourless oil, R_f 0.78 (dichloromethane); ν_{max}(film)/cm^{-1} 2950, 2930, 2867, 1586, 1452; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=7.5 Hz, 2′-Me), 1.61 (1H, ddq, *J*=13.9, 8.8, 7.5 Hz, 1′-H_a), 1.73 (1H, dddd, *J*=13.4, 6.5, 3.1, 2.9 Hz, 4-H_a), 1.89 (1H, dqd, *J*=13.9, 7.5, 3.6 Hz, 1′-H_b), 2.24 (1H, dddd, *J*=13.4, 9.6, 7.6, 6.2 Hz, 4-H_b), 2.47 (3H, s, Ar-Me), 3.37 (1H, ddd, *J*=9.6, 9.6, 6.5 Hz, 5-H_a), 3.46–3.58 (3H, m, 2-H, 3-H, 5-H_b), 7.24–7.36 (7H, m), 7.73 (2H, d, *J*=8.3 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 10.0 (2′-Me), 21.6 (Ar-Me), 29.5 (1′-CH_2), 30.6 (4-CH_2), 44.1 (3-CH), 47.8 (5-CH_2), 67.8 (2-CH), 127.9 (ArCH), 128.0 (ArCH), 129.1 (ArCH), 129.6 (ArCH), 131.5 (ArC), 133.6 (ArC), 134.7 (ArCH), 143.2 (ArC); *m/z* (FAB) 410 (M^++1, 66%), 380 (48), 252 (97), 184 (100), 155 (76), 91 (79), 69 (54). Found: M^++1, 410.0697. $C_{19}H_{24}NO_2SSe$ requires: M, 410.0693.

3.2.2. (2*RS*,3*SR*,5*RS*)-5-Ethyl-2-pentyl-3-phenylselanyl-1-tosylpyrrolidine 29. (*E*)-Homoallylic tosylamide **28** (100 mg, 0.4 mmol) in dichloromethane (2 ml) was subjected to the general cyclisation conditions A to give an orange oil, which was purified by column chromatography (dichloromethane) to give the *title compound* **29** (102 mg, 80%) as a pale yellow oil, R_f 0.53 (dichloromethane); ν_{max}(film)/cm^{-1} 3050, 2940, 2870, 1590, 1465; δ_H (250 MHz, $CDCl_3$) 0.92 (3H, t, *J*=6.9 Hz, 5′-Me), 0.98 (3H, t, *J*=7.2 Hz,

2″-Me), 1.01–1.49 (10H, m), 2.00 (1H, ddd, *J*=14.2, 3.3, 1.9 Hz, 4-H_a), 2.45 (3H, s, Ar-Me), 2.59 (1H, ddd, *J*=14.2, 8.7, 7.5 Hz, 4-H_b), 3.59 (1H, ddd, *J*=7.5, 1.9, 1.4 Hz, 3-H), 3.78 (1H, dddd, *J*=11.3, 8.7, 3.3, 3.3 Hz, 5-H), 3.93 (1H, ddd, *J*=10.1, 2.9, 1.4 Hz, 2-H), 7.28–7.50 (7H, m), 7.80 (2H, d, *J*=8.3 Hz, 2×ArH); δ_C (67.8 MHz, $CDCl_3$) 10.0 (Me), 14.1 (Me), 21.6 (Ar-Me), 22.5 (CH_2), 25.7 (CH_2), 27.3 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 34.6 (4-CH_2), 43.7 (3-CH), 61.6 (5-CH), 69.5 (2-CH), 126.9 (ArCH), 127.9 (ArCH), 128.0 (ArC), 129.2 (ArCH), 129.7 (ArCH), 134.7 (Ar-CH), 142.9 (ArC), 143.5 (ArC); *m/z* (FAB) 478 (M^++1, 16%), 322 (30), 212 (100), 155 (35), 91 (43). Found: M^++1, 480.1480. $C_{24}H_{34}NO_2SSe$ requires: M, 480.1475.

3.2.3. (2*RS*,3*SR*,4*RS*,5*SR*)-4,5-Dimethyl-3-phenylselanyl-2-propyl-1-tosylpyrrolidine 39. Using general procedure A, (2*SR*, 3*SR*)-(*E*)-homoallylic tosylamide **38** (20 mg, 0.07 mmol) was cyclised to afford the *title compound* **39** (30 mg, 84%), following column chromatography (dichloromethane), as a pale yellow oil, R_f 0.56 (dichloromethane); ν_{max}(film)/cm^{-1} 2966, 2931, 2868, 1475, 1342; δ_H (250 MHz, $CDCl_3$) 0.96 (3H, t, *J*=7.2 Hz, 3′-Me), 1.01 (3H, d, *J*=6.9 Hz, 4-Me), 1.14 (3H, d, *J*=6.9 Hz, 5-Me), 1.29–1.42 (1H, m, 4-H), 1.49–1.65 (2H, m, 2′-CH_2), 1.88–2.01 (2H, m, 1′-CH_2), 2.42 (3H, s, Ar-Me), 2.81 (1H, dd, *J*=11.4, 8.3 Hz, 3-H), 3.46 (1H, ddd, *J*=8.3, 5.1, 4.6 Hz, 2-H), 3.72 (1H, dq, *J*=7.2, 6.9 Hz, 5-H), 7.11–7.62 (9H, m); δ_C (67.8 MHz, $CDCl_3$) 12.8 (3′-Me), 14.2 (4-Me), 17.2 (2′-CH_2), 17.6 (5-Me), 21.5 (Ar-Me), 35.2 (1′-CH_2), 40.8 (4-CH), 49.6 (3-CH), 56.1 (5-CH), 65.7 (2-CH), 127.7 (ArC), 129.0 (ArCH), 129.2 (ArCH), 129.6 (ArCH), 131.5 (ArCH), 134.4 (ArC), 136.7 (ArCH), 142.8 (ArC); *m/z* (FAB) 451 (M^+, 69%), 408 (45), 198 (100), 155 (58), 91 (84), 77 (18), 68 (23). Found: M^+, 451.1086. $C_{22}H_{29}NO_2SSe$ requires: M, 451.1084.

3.2.4. (2*RS*,3*SR*,4*RS*,5*RS*)-4,5-Dimethyl-3-phenylselanyl-2-propyl-1-tosylpyrrolidine 41. Using general procedure A, (2*RS*, 3*SR*)-(*E*)-homoallylic tosylamide **40** (20 mg, 0.07 mmol) was cyclised to afford the *title compound* **41** (28 mg, 84%), following column chromatography (dichloromethane), as a pale yellow oil, R_f 0.58 (dichloromethane); ν_{max}(film)/cm^{-1} 2966, 2931, 2868, 1590, 1475, 1342; δ_H (250 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.2 Hz, 3′-Me), 1.04 (3H, d, *J*=6.5 Hz, 4-Me), 1.11 (3H, d, *J*=6.6 Hz, 5-Me), 1.17–1.98 (5H, m), 2.43 (3H, s, Ar-Me), 2.88 (1H, dd, *J*=8.7, 5.3 Hz, 3-H), 3.28 (1H, dq, *J*=8.3, 6.6 Hz, 5-H), 4.11 (1H, ddd, *J*=7.6, 5.3, 4.2 Hz, 2-H), 7.13–7.62 (9H, m); δ_C (67.8 MHz, $CDCl_3$) 14.0 (3′-Me), 16.6 (4-Me), 17.1 (5-Me), 18.1 (2′-CH_2), 21.5 (Ar-Me), 37.2 (1′-CH_2), 48.1 (4-CH), 50.9 (3-CH), 62.3 (5-CH), 68.0 (2-CH), 126.8 (ArCH), 128.5 (ArCH), 129.2 (ArCH), 129.3 (ArC), 131.5 (ArCH), 136.3 (ArCH), 140.5 (ArC), 142.5 (ArC); *m/z* (FAB) 451 (M^+, 35%), 408 (45), 198 (100), 155 (59), 91 (84), 77 (18), 68 (24). Found: M^+, 451.1110. $C_{22}H_{29}NO_2SSe$ requires: M, 451.1084.

3.2.5. (2*SR*,3*RS*,5*SR*)-5-Ethyl-2-phenyl-3-phenylselanyl-1-tosylpyrrolidine 31. A stirred mixture of (*E*)-homoallylic tosylamide **30** (0.28 g, 0.86 mmol), anhydrous potassium carbonate (0.12 g, 0.86 mmol) and water (10 μl) in dichloromethane (5 ml) was maintained at −78 °C for 20 min before the portionwise addition of phenylselanyl chloride (0.18 g, 0.94 mmol). After a further 0.5 h, the cooling bath was removed and the mixture allowed to warm to ambient temperature, then the solvents were largely evaporated. The residue was separated by column chromatography (dichloromethane) to give the 2,5-*trans* isomer **31** (0.32 g, 83%) as a yellow oil, R_f 0.28 (hexane–EtOAc, 10:1); ν_{max}(film)/cm^{-1} 3030, 2960, 2930, 2880, 1590, 1455, 1340; δ_H (250 MHz, $CDCl_3$) 0.87 (3H, t, *J*=7.6 Hz, 2′-Me), 1.66–1.83 (2H, m, 1′-CH_2), 2.04 (1H, ddd, *J*=12.8, 2.5, 2.5 Hz, 4-H_b), 2.36 (3H, s, Ar-Me), 2.63 (1H, ddd, *J*=12.8, 7.6, 6.4 Hz, 4-H_a), 3.61 (1H, ddd, *J*=7.6, 2.5, 2.1 Hz, 3-H), 4.07–4.11 (1H, m, 5-H), 5.03 (1H, d, *J*=2.1 Hz, 2-H), 7.14–7.34 (12H, m), 7.59 (2H, d, *J*=8.2 Hz, 2×ArH); δ_C (67.8 MHz, $CDCl_3$) 11.3 (2′-Me), 21.1 (Ar-Me), 28.0 (1′-CH_2), 33.8 (4-CH_2), 48.1 (3-CH), 63.4 (5-CH), 72.4 (2-CH), 126.4 (ArCH), 126.9 (ArCH), 127.5 (ArCH), 128.4 (ArCH), 129.0 (ArCH), 129.9 (ArCH), 134.6 (ArCH), 134.8 (ArC), 135.3 (ArCH), 139.5 (ArC), 141.7 (ArC), 142.6 (ArC). Found (EI): M^+, 485.0927. $C_{25}H_{27}NO_2SSe$ requires: M, 485.0928.

The sample was contaminated with ca. 6% of the corresponding 2,5-*cis* isomer **32** (following compound).

3.2.6. (2*RS*,3*SR*,5*SR*)-5-Ethyl-2-phenyl-3-phenylselanyl-1-tosylpyrrolidine 32. To a stirred solution of (*E*)-homoallylic tosylamide **30** (50 mg, 0.14 mmol) in dichloromethane (1 ml) maintained at −78 °C was added phenylselanyl chloride (30 mg, 0.15 mmol). After 5 min at this temperature, one drop of 10 M hydrochloric acid was added. After a further 0.5 h, the cooling bath was removed and the mixture allowed to warm to ambient temperature, then the solvents were largely evaporated. The residue was separated by column chromatography (dichloromethane) to give the 2,5-*cis* isomer **32** (61 mg, 77%) as a yellow oil, R_f 0.28 (hexanes–EtOAc, 9:1); ν_{max}(film)/cm^{-1} 3025, 2950, 2925, 2877, 1590, 1455, 1340; δ_H (250 MHz, $CDCl_3$) 0.99 (3H, t, *J*=7.4 Hz, 2′-Me), 1.61–1.71 (2H, m, 1′-CH_2), 2.02 (1H, ddd, *J*=13.2, 5.6, 5.2 Hz, 4-H_a), 2.23 (1H, ddd, *J*=13.2, 7.6, 4.8 Hz, 4-H_b), 2.44 (3H, s, Ar-Me), 3.47 (1H, ddd, *J*=7.6, 5.9, 5.6 Hz, 3-H), 3.79–3.83 (1H, m, 5-H), 4.58 (1H, d, *J*=5.9 Hz, 2-H), 7.18–7.36 (12H, m), 7.62 (2H, d, *J*=8.3 Hz, 2×ArH); δ_C (67.8 MHz, $CDCl_3$) 10.9 (2′-Me), 21.5 (Ar-Me), 29.4 (1′-CH_2), 36.7 (4-CH_2), 47.9 (3-CH), 62.6 (5-CH), 70.6 (2-CH), 126.4 (ArCH), 126.6 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 129.1 (ArC), 129.5 (ArCH), 134.8 (ArC), 141.3 (ArC), 143.1 (ArC). Found: M^+, 485.0930.

3.3. Oxidative elimination of phenylselanyl group: general procedure B

To a stirred solution of a phenylselanyl pyrrolidine (1 mmol) in tetrahydrofuran (1 ml) was added aqueous hydrogen peroxide (30%, 0.2 ml) and the resulting solution stirred at ambient temperature for 1 h. The bulk of the solvent was evaporated, the residue dissolved in dichloromethane (2 ml) and the resulting solution washed with water (3×1 ml) then dried, filtered through a short plug of silica gel and evaporated to leave essentially pure pyrroline.

3.3.1. (2*RS*,5*SR*)-4,5-Dimethyl-2-propyl-1-tosyl-3-pyrroline 46. Oxidation of 4,5-*syn*-dimethyl pyrrolidine **39** (20 mg) gave the 2,5-*cis*-pyrroline **46** (11 mg, 86%) as

a colourless viscous oil, R_f 0.67 (dichloromethane); ν_{max} (film)/cm^{-1} 3060, 2950, 1580, 1420, 1340; δ_H (250 MHz, $CDCl_3$) 0.93 (3H, t, J=7.3 Hz, 3′-Me), 1.39 (3H, d, J=6.5 Hz, 5-Me), 1.57 (3H, d, J=0.8 Hz, 4-Me), 1.26–1.78 (4H, m, 1′-, 2-CH_2), 2.42 (3H, s, Ar-Me), 4.24–4.29 (1H, m, 2-H), 4.40 (1H, qd, J=6.5, 0.8 Hz, 5-H), 5.15–5.17 (1H, m, 3-H), 7.28 (2H, d, J=8.3 Hz, 2×ArH), 7.69 (2H, d, J=8.3 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 13.5 (3′-Me), 14.1 (4-Me), 18.4 (2′-CH_2), 21.4 (Ar-Me), 22.1 (5-Me), 39.9 (1′-CH_2), 65.6 (5-CH), 66.9 (2-CH), 122.6 (ArCH), 127.6 (4-C), 127.7 (3-CH), 129.6 (ArCH), 138.6 (ArC), 143.2 (ArC); m/z (ES) 294 (M^++1, 100%), 145 (22), 104 (21), 102 (18), 83 (23), 60 (69). Found: M^++1, 294.1528. $C_{16}H_{24}NO_2S$ requires: M, 294.1532.

3.3.2. (2*RS*,5*RS*)-4,5-Dimethyl-2-propyl-1-tosyl-3-pyrroline 47. Oxidation of 4,5-*anti*-dimethyl pyrrolidine **41** (20 mg) gave 2,5-*trans*-pyrroline **47** (10 mg, 80%) as a colourless viscous oil, R_f 0.65 (dichloromethane); ν_{max}(film)/cm^{-1} 3060, 2950, 1580, 1420, 1340; δ_H (250 MHz, $CDCl_3$) 0.85 (3H, t, J=7.3 Hz, 3′-Me), 1.35 (3H, d, J=6.4 Hz, 5-Me), 1.65 (3H, s, 4-Me), 1.11–1.91 (4H, m, 1′-, 2-CH_2), 2.41 (3H, s, Ar-Me), 4.36–4.43 (1H, m, 5-H), 4.48–4.56 (1H, m, 2-H), 5.26–5.27 (1H, m, 3-H), 7.28 (2H, d, J=8.3 Hz, 2×ArH), 7.73 (2H, d, J=8.3 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 14.0 (3′-Me), 17.7 (4-Me), 19.2 (2′-CH_2), 19.4 (5-Me), 21.4 (Ar-Me), 36.9 (1′-CH_2), 65.7 (5-CH), 66.5 (2-CH), 122.7 (ArCH), 126.8 (3-CH), 129.3 (ArCH), 134.3 (ArC), 138.2 (ArC); m/z (ES) 294 (M^++1, 100%), 198 (7), 153 (10), 102 (18), (23). Found: M^++1, 294.1529. $C_{16}H_{24}NO_2S$ requires: M, 294.1532.

3.3.3. (2*SR*,5*RS*)-5-Ethyl-2-phenyl-1-tosyl-3-pyrroline 48. Following general procedure B, oxidation of phenylselanyl pyrrolidine **31** (20 mg) gave 2,5-*trans*-pyrroline **48** (10 mg, 84%) as a colourless, viscous oil, R_f 0.48 (dichloromethane); ν_{max}(film)/cm^{-1} 3050, 2950, 1590, 1430, 1340; δ_H (270 MHz, $CDCl_3$) 0.88 (3H, t, J=7.2 Hz, 2′-Me), 1.85–2.14 (2H, m, 1′-CH_2), 2.23 (3H, s, Ar-Me), 4.57–4.69 (1H, m, 5-H), 5.50 (1H, app. ddd, J=5.3, 2.0, 1.9 Hz, 2-H), 5.58 (1H, ddd, J=6.3, 2.0, 1.8 Hz, 4-H), 5.69 (1H, ddd, J=6.3, 1.9, 1.6 Hz, 3-H), 6.83–7.19 (9H, m); δ_C (67.5 MHz, $CDCl_3$) 8.0 (2′-Me), 21.3 (Ar-Me), 28.4 (1′-CH_2), 67.7 (5-CH), 71.6 (2-CH), 126.4 (ArCH), 127.8 (ArCH), 127.9 (ArCH), 128.7 (ArCH), 128.9 (4-CH), 129.0 (3-CH), 129.9 (ArCH), 137.7 (ArC), 138.1 (ArC), 141.8 (ArC); m/z (ES) 328 (M^++1, 100%), 245 (8), 157 (9), 102 (9). Found: M^++1, 328.1372. $C_{19}H_{22}NO_2S$ requires: M, 328.1376.

3.3.4. (2*SR*,5*SR*)-5-Ethyl-2-phenyl-1-tosyl-3-pyrroline 49. Following general procedure B, oxidation of phenylselanyl pyrrolidine **32** (20 mg) gave 2,5-*cis*-pyrroline **49** (10 mg, 81%) as a colourless viscous oil, R_f 0.47 (dichloromethane); ν_{max}(film)/cm^{-1} 3050, 2950, 1590, 1430, 1340; δ_H (270 MHz, $CDCl_3$) 0.90 (3H, t, J=7.6 Hz, 2′-Me), 1.53–1.99 (2H, m, 1′-CH_2), 2.33 (3H, s, Ar-Me), 4.38–4.46 (1H, m, 5-H), 5.40 (1H, app. ddd, J=2.0, 2.0, 2.0 Hz, 2-H), 5.56 (1H, ddd, J=6.3, 2.0, 1.9 Hz, 4-H), 5.68 (1H, ddd, J=6.3, 2.0, 1.9 Hz, 3-H), 7.15–7.32 (7H, m), 7.56 (2H, d, J=8.2 Hz, 2×ArH); δ_C (67.5 MHz, $CDCl_3$) 10.6 (2′-Me), 21.9 (Ar-Me), 30.8 (1′-CH_2), 69.8 (5-CH), 71.1 (2-CH), 127.7 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 129.1 (4-CH), 129.7 (3-CH), 130.0 (ArCH), 135.7 (ArC), 141.3 (ArC), 143.8 (ArC); m/z (ES) 328 (M^++1, 100%), 245 (7), 157 (9), 102 (11). Found: M^++1, 328.1371. $C_{19}H_{22}NO_2S$ requires: M, 328.1376.

3.4. Pyrrolidine carboxylate formation and derivatives

3.4.1. Methyl (2*SR*,4*RS*,5*SR*)-5-phenyl-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 52. To a stirred solution of cinnamyl tosylamide **51** (0.22 g, 0.60 mmol) in dry dichloromethane (5 ml) at ambient temperature was added phenylselanyl bromide (0.285 g, 1.21 mmol) in one portion and the resulting solution stirred for 72 h then filtered through silica, eluted first with toluene to remove excess selanyl bromide. Further elution with dichloromethane provided the product, which was crystallised from toluene–hexane to give 2,5-*cis*-pyrrolidine carboxylate **52** (0.279 g, 90%) as colourless crystals, mp 128–130 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 2950, 2910, 1740, 1450; δ_H (400 MHz, DMSO-d_6) 1.89 (1H, app. dt, J=13.2, 7.5 Hz, 3-H_a), 2.36 (1H, app. dt, J=ca. 13.2, 5.9 Hz, 3-H_b), 2.43 (3H, s, Ar-Me), 3.63 (1H, app. q, J=ca. 6.3 Hz, 4-H), 3.77 (3H, s, OMe), 4.34 (1H, d, J=5.4 Hz, 5-H), 4.47 (1H, dd, J=7.5, 6.2 Hz, 2-H), 7.26–7.38 (8H, m), 7.40 (2H, d, J=8.2 Hz), 7.49 (2H, d, J=7.4 Hz), 7.59 (2H, d, J=8.2 Hz); δ_C (100 MHz, DMSO-d_6) 21.6 (Ar-Me), 35.6 (3-CH_2), 47.8 (4-CH), 53.0 (OMe), 61.5 (5(2)-CH), 69.9 (2(5)-CH), 126.8 (ArC), 127.5 (2×ArCH), 128.0 (2×ArCH), 128.6 (2×ArCH), 128.9 (ArCH), 129.9 (2×ArCH), 130.4 (2×ArCH), 133.7 (ArC), 135.5 (2×ArCH), 141.1 (ArC), 144.5 (ArC), 172.3 (C=O) [one ArCH obscured]; m/z (APCI) 516 (M^++1, 100%). Found: M^++1, 516.0750. $C_{25}H_{26}NO_4SSe$ requires: M, 516.0748.

3.4.2. Methyl (2*SR*,4*SR*,5*RS*)-5-phenyl-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 53. Most experiments resulted in the formation of mixtures (see Section 2). In one of the more reproducible cyclisations, to a stirred solution of cinnamyl tosylamide **51** (0.205 g, 0.57 mmol) in dry dichloromethane (4 ml) maintained at −78 °C and containing anhydrous potassium carbonate (0.087 g, 0.63 mmol) was added phenylselanyl chloride (0.12 g, 0.63 mmol) in one portion and the resulting solution stirred for1 h at this temperature then allowed to warm to ambient temperature. The bulk of the solvent was removed and the residue separated as described above for the 2,5-*cis* isomer to give 2,5-*trans*-pyrrolidine carboxylate **53** containing 23% of the 2,5-*cis* isomer **52** (0.252 g, 86%) as an oil. The 2,5-*trans* isomer **53** showed δ_H (400 MHz, DMSO-d_6) 2.16 (1H, app. dt, J=14.2, 3.5 Hz, 3-H_a), 2.32 (3H, s, Ar-Me), 3.09 (1H, app. dt, J=14.2, 8.6 Hz, 3-H_b), 3.67–3.71 (1H, obscured m, contains J=4.7 Hz, 4-H), 3.69 (3H, s, OMe), 4.79 (1H, d, J=4.7 Hz, 5-H), 4.88 (1H, dd, J=8.6, 3.5 Hz, 2-H), 6.91 (2H, d, J=7.3 Hz, 2×ArH), 7.03 (2H, t, J=7.7 Hz, 2×ArH), 7.12 (2H, dd, J=8.2, 6.9 Hz, 2×ArH), 7.17 (2H, t, J=8.2 Hz, 2×ArH), 7.26–7.32 (4H, m), 7.39 (2H, dd, J=6.9, 1.3 Hz, 2×ArH); δ_C (100 MHz, DMSO-d_6) 21.4 (Ar-Me), 36.7 (3-CH_2), 48.1 (4-CH), 52.6 (OMe), 62.3 (5(2)-CH), 70.8 (2(5)-CH), 127.1 (2×ArCH), 128.1 (2×ArCH), 128.4 (2×ArCH), 129.3 (2×ArCH), 129.8 (2×ArCH), 130.1 (ArCH), 133.7 (ArC), 134.3 (2×ArCH), 139.2 (ArC), 142.9 (ArC), 172.8 (C=O) [one ArCH and one ArC obscured]; m/z (APCI) 516 (M^++1, 100%).

Alternatively, cinnamyl tosylamide **51** (0.217 g, 0.604 mmol) and anhydrous potassium carbonate (0.21 g,

1.5 mmol) were stirred together in dry acetonitrile (1 ml) at −78 °C then phenylselanyl chloride (0.21 g, 1.1 mmol) was added portionwise. After 1 h at this temperature, the mixture was stirred for 16 h without further cooling. Dichloromethane (10 ml) was then added, the mixture filtered and the filtrate evaporated. Analysis of the residue by proton NMR showed a 2,5-*trans*/*cis* ratio of 88:12 [**53**:**52**]. The weight of the otherwise clean product indicated a combined yield of 87%.

3.4.3. Methyl (2*SR*,5*RS*)-5-phenyl-1-tosyl-3-pyrroline-2-carboxylate 54. Oxidation of 2,5-*cis*-5-phenyl carboxylate **52** (0.17 g, 0.33 mmol) according to general procedure B gave 2,5-*cis*-pyrroline carboxylate **54** (0.11 g, 92%) as a colourless solid, mp 119–121 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3025, 2952, 1758, 1597, 1494, 1455, 1352, 1165, 1092; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, Ar-Me), 3.77 (3H, s, OMe), 5.36–5.39 (1H, m, 5-H), 5.57–5.60 (1H, m, 2-H), 5.73–5.79 (2H, m, 3-, 4-H), 7.10 (2H, d, J=8.2 Hz, 2×ArH), 7.18–7.24 (3H, m), 7.35 (2H, dd, J=ca. 7.5, 1.8 Hz, 2×*o*-ArH), 7.53 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (ArMe), 52.7 (OMe), 68.5 (3(4)-CH), 71.0 (4(3)-CH), 123.0 (CH), 127.6 (2×ArCH), 127.8 (CH), 127.9 (2×ArCH), 128.4 (2×s ArCH), 129.2 (2×ArCH), 133.1 (CH), 135.6 (ArC), 139.2 (ArC), 143.5 (ArC), 170.3 (C=O); *m*/*z* (ES) 358 (M^++1, 100%), 298 (38), 203 (31). Found: M^++1, 358.1109. $C_{19}H_{20}NO_4S$ requires: M, 358.1113.

3.4.4. Methyl (2*RS*,4*RS*,5*SR*)-5-(furan-2-yl)-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 56. Tosylamide **55** (0.35 g, 1.0 mmol) and anhydrous potassium carbonate (0.21 g, 1.5 mmol) were stirred together in dry tetrahydrofuran (1 ml) at −78 °C and phenylselanyl chloride (0.21 g, 1.1 mmol) in tetrahydrofuran (1 ml) was added dropwise. After stirring for 2 h at this temperature, the bulk of the solvent was evaporated and the residue separated by column chromatography (hexanes–EtOAc, 6:1) to give 2,5-*trans*-pyrrolidine-2-carboxylate **56** (0.42 g, 83%) as a colourless solid, mp 89–92 °C (hexane–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2963, 2922, 1748, 1438, 1159, 1098; δ_H (400 MHz, $CDCl_3$) 2.31 (1H, ddd, J=13.8, 4.3, 4.3 Hz, 3-H_a), 2.37 (3H, s, Ar-Me), 3.01 (1H, ddd, J=13.8, 8.7, 8.7 Hz, 3-H_b), 3.72–3.76 (1H, m, 4-H), 3.84 (3H, s, OMe), 4.57 (1H, dd, J=8.7, 4.3 Hz, 2-H), 5.05 (1H, d, J=4.8 Hz, 5-H), 6.18 (1H, dd, J=3.1, 1.9 Hz, 4′-H), 6.26 (1H, d, J=3.1 Hz, 3′-H), 6.85 (1H, d, J=1.9 Hz, 5′-H), 7.10–7.35 (9H, m); δ_C (100 MHz, $CDCl_3$) 22.0 (ArMe), 37.5 (3-CH_2), 45.0 (4-CH), 53.5 (OMe), 61.0 (2-CH), 63.0 (5-CH), 111.5 (4′-CH), 113.0 (3′-CH), 127.8 (ArCH), 128.3 (ArCH), 130.1 (ArCH), 130.3 (ArCH), 134.8 (ArC), 135.0 (ArCH), 135.1 (ArC), 143.0 (ArC), 152.0 (ArC), 171.5 (C=O); *m*/*z* (EI) 505 (M^+, 7%), 350 (7), 192 (9), 155 (16), 134 (16), 92 (100). Found: M^+, 505.0462. $C_{23}H_{23}NO_5SSe$ requires: M, 505.0462.

3.4.5. Methyl (2*RS*,4*SR*,5*RS*)-5-(furan-2-yl)-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 57. Tosylamide **55** (0.35 g, 1.0 mmol) and anhydrous potassium carbonate (0.21 g, 1.5 mmol) were stirred together in dry acetonitrile (1 ml) at ambient temperature and phenylselanyl chloride (0.21 g, 1.1 mmol) was added portionwise. After stirring for 2 h at this temperature, the bulk of the solvent was evaporated and the residue separated by column chromatography (hexanes–EtOAc, 6:1) to give 2,5-*cis*-pyrrolidine-2-carboxylate **57** (0.43 g, 85%) as a colourless crystalline solid, mp 98–99 °C (hexane–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2952, 1756, 1598, 1438, 1355, 1290, 1203, 1161, 1095, 1023; δ_H (400 MHz, $CDCl_3$) 2.17 (1H, ddd, J=13.2, 7.4, 5.1 Hz, 3-H_a), 2.35 (3H, s, Ar-Me), 2.50 (1H, ddd, J=13.2, 7.4, 6.0 Hz, 3-H_b), 3.78 (3H, s, OMe), 3.83–3.87 (1H, m, 4-H), 4.61 (1H, dd, J=7.4, 7.4 Hz, 2-H), 4.82 (1H, d, J=3.9 Hz, 5-H), 6.25 (1H, dd, J=3.2, 1.9 Hz, 4′-H), 6.51 (1H, d, J=ca. 3.2 Hz, 3′-H), 7.25–7.40 (8H, m), 7.64 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (ArMe), 35.6 (3-CH_2), 43.8 (4-CH), 52.5 (OMe), 60.6 (2-CH), 63.7 (5-CH), 109.3 (4′-CH), 110.4 (3′-CH), 127.4 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 129.2 (ArCH), 129.4 (ArCH), 134.5 (ArC), 135.1 (ArC), 142.2 (5′-CH), 143.8 (ArC), 151.9 (ArC), 171.9 (C=O); *m*/*z* (EI) 505 (M^+, 32%), 446 (15), 275 (21), 192 (95), 166 (59), 155 (86), 133 (100), 106 (70), 90 (87). Found: M^+, 505.0462. $C_{23}H_{23}NO_5SSe$ requires: M, 505.0462. Anal. Calcd for $C_{23}H_{23}NO_5SSe$: C, 54.76; H, 4.60; N, 2.78. Found: C, 54.88; H, 4.74; N, 3.02%.

3.4.6. Methyl (2*RS*,5*SR*)-5-(furan-2-yl)-1-tosyl-3-pyrroline-2-carboxylate 58. To a stirred solution of 2,5-*cis*-selanyl-pyrrolidine **57** (0.40 g, 0.79 mmol) in tetrahydrofuran (5 ml) was added aqueous hydrogen peroxide (30%, 0.2 ml, 2.5 equiv). After 2 h at ambient temperature, the bulk of the solvent was evaporated and the residue dissolved in dichloromethane (10 ml) and water (10 ml). The separated organic solution was washed with water (2×10 ml) then dried and evaporated. Column chromatography of the residue (hexanes–EtOAc, 4:1) gave 2,5-*cis*-pyrroline **58** (0.21 g, 76%) as a colourless crystalline solid, mp 129–131 °C (hexanes–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2955, 1760, 1598, 1434, 1351, 1166; δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, Ar-Me), 3.79 (3H, s, OMe), 5.39 (1H, dd, J=4.5, 2.2 Hz, 2-H), 5.77 (1H, dd, J=4.0, 2.0 Hz, 5-H), 5.89–6.01 (2H, m, 3-, 4-H), 6.28 (1H, dd, J=3.2, 1.8 Hz, 4′-H), 6.30 (1H, d, J=3.2 Hz, 3′-H), 7.25 (2H, d, J=8.2 Hz, 2×ArH), 7.33 (1H, app. br s, 5′-H), 7.71 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (ArMe), 52.7 (OMe), 63.8 (5-CH), 67.9 (2-CH), 108.6 (3′-CH), 110.5 (4′-CH), 124.9 (3(4)-CH), 127.7 (2×ArCH), 129.3 (2×ArCH), 129.7 (4(3)-CH), 135.9 (ArC), 142.5 (5′-CH), 143.6 (ArC), 151.8 (ArC), 170.0 (C=O); *m*/*z* (EI) 347 (M^+, 2%), 288 (100), 192 (34), 155 (90), 132 (84), 104 (74), 77 (49), 65 (85). Found: M^+, 347.0828. $C_{17}H_{17}NO_5S$ requires: M, 347.0827. Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.93; H, 4.79; N, 4.36%.

3.4.7. Methyl (2*RS*,5*RS*)-5-(furan-2-yl)-1-tosyl-3-pyrroline-2-methanol 59. The foregoing ester **58** (0.15 g, 0.43 mmol) was stirred in dry toluene (1 ml), cooled in an ice bath for 10 min before the dropwise addition of diisobutylaluminium hydride in toluene (0.6 ml of a 1.5 M solution, 0.91 mmol). The resulting mixture was stirred for 3 h then quenched by the careful addition of methanol (0.2 ml) followed by 2 M hydrochloric acid (2 ml). The resulting mixture was filtered, the solids washed with toluene and the filtrate separated into organic and aqueous layers. The latter was extracted with ether (3×5 ml) and the extracts combined with the organic layer from the original filtrate. The resulting

organic solution was dried, filtered and evaporated. Column chromatography of the residue (hexanes–EtOAc, 2:1) separated the pyrroline-methanol **59** (0.10 g, 75%) as a colourless oil, ν_{max}(film)/cm^{-1} 3450; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, Ar-Me), 3.66 (1H, dd, J=11.6, 3.1 Hz, 1′-H_a), 3.77 (1H, dd, J=11.6, 3.1 Hz, 1′-H_b), 4.54–4.57 (1H, m, 2-H), 5.51 (1H, d, J=1.7 Hz, 5-H), 5.63–5.67 (2H, m, 3-, 4-H), 6.24–6.28 (2H, m, 3′-, 4′-H), 7.23 (2H, d, J=8.2 Hz, 2×ArH), 7.34 (1H, app. br s, 5′-H), 7.67 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (ArMe), 58.2 (2-CH), 64.2 (5-CH), 65.3 (1′-CH_2), 108.0 (3′-CH), 110.0 (4′-CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 129.8 (CH) 134.5 (C), 142.6 (5′-CH), 144.0 (C), 152.6 (C). m/z (APCI) found: M^++1 (100%), 320.0959. $C_{16}H_{18}NO_4S$ requires: M, 320.0957.

3.4.8. Methyl (2*SR*,3*RS*,4*SR*,5*SR*)-3,4-diacetyloxy-5-(furan-2-yl)-1-tosylpyrrolidine-2-carboxylate 60. Pyrroline-2-carboxylate **58** (0.10 g, 0.29 mmol) was stirred in aqueous acetone (1:5; 2 ml) containing *N*-methylmorpholine-*N*-oxide (0.071 g, 0.60 mmol) at ambient temperature and osmium tetroxide (0.15 ml of a 5% solution in *t*-BuOH, 0.03 mmol) was added and the resulting solution stirred for 16 h then concentrated. The residue was dissolved in dry pyridine (2 ml) and acetic anhydride (0.06 ml, 0.60 mmol) was added. After a further 20 h at ambient temperature, 2 M hydrochloric acid (5 ml) was added and the resulting mixture extracted with dichloromethane (3×10 ml). The combined extracts were washed with brine (10 ml) then dried and evaporated. Column chromatography of the residue (hexanes–EtOAc, 6:1) separated the diacetate **60** (0.085 g, 64%) as an oil, ν_{max}(film)/cm^{-1} 2950, 1748, 1598, 1440, 1352, 1164, 1120, 1090; δ_H (400 MHz, $CDCl_3$) 1.78 (3H, s, OAc), 2.01 (3H, s, OAc), 2.42 (3H, s, Ar-Me), 3.81 (3H, s, OMe), 4.37 (1H, d, J=6.7 Hz, 2-H), 4.86 (1H, d, J=3.0 Hz, 5-H), 5.40 (1H, dd, J=3.6, 3.6 Hz, 4-H), 5.54 (1H, dd, J=6.7, 3.6 Hz, 5-H), 6.29 (1H, dd, J=3.2, 1.9 Hz, 4′-H), 6.55 (1H, d, J=3.2 Hz, 3′-H), 7.31 (2H, d, J=8.2 Hz, 2×ArH), 7.34 (1H, app. br s, 5′-H), 7.70 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 20.3 (Me), 20.4 (Me), 21.6 (ArMe), 53.1 (OMe), 60.6 (5-CH), 62.6 (2-CH), 72.6 (3-CH), 73.1 (4-CH), 110.1 (3′-CH), 110.7 (4′-CH), 128.0 (CH), 129.6 (CH), 134.2 (C), 143.1 (5′-CH), 144.1 (C), 149.1 (C), 169.2 (C═O), 169.3 (C═O), 169.8 (C═O); m/z (APCI) found: M^++1 (100%), 466.1174. $C_{21}H_{24}NO_9S$ requires: M, 466.1172.

3.4.9. (2*SR*,3*RS*,4*SR*,5*SR*)-2-Acetyloxymethyl-3,4-diacetyloxy-5-(furan-2-yl)-1-tosylpyrrolidine 61. Pyrroline-2-methanol **59** (50 mg, 0.157 mmol) was stirred in aqueous acetone (1:5, 2 ml) containing *N*-methylmorpholine-*N*-oxide (39 mg, 0.33 mmol) at ambient temperature and osmium tetroxide (80 μl of a 5% solution in *t*-BuOH, 0.015 mmol) was added and the resulting solution stirred for 16 h then concentrated. The residue was dissolved in dry pyridine (2 ml) and acetic anhydride (33 μl, 0.60 mmol) was added. After a further 20 h at ambient temperature, 2 M hydrochloric acid (5 ml) was added and the resulting mixture extracted with dichloromethane (3×10 ml). The combined extracts were washed with brine (10 ml) then dried and evaporated. Column chromatography of the residue (hexanes–EtOAc, 6:1) separated the triacetate **61** (40 mg, 55%) as a colourless solid, mp 76–78 °C (hexane–ether), ν_{max}(film)/cm^{-1} 2950, 1756, 1360, 1212, 1167; δ_H (400 MHz, $CDCl_3$) 1.78 (3H, s, OAc), 1.94 (3H, s, OAc), 2.06 (3H, s, OAc), 2.45 (3H, s, Ar-Me), 3.81–4.22 (1H, m, 2-H), 4.37 (1H, dd, J=11.8, 8.5 Hz, CH_aH$_b$OAc), 4.46 (1H, dd, J=11.8, 5.6 Hz, CH$_a$$H_b$OAc), 4.78 (1H, d, J=4.7 Hz, 5-H), 5.38 (1H, dd, J=4.7, 4.7 Hz, 3-H), 5.48 (1H, dd, J=4.7, 4.7 Hz, 4-H), 6.33 (1H, dd, J=3.3, 1.5 Hz, 4′-H), 6.42 (1H, d, J=3.3 Hz, 3′-H), 7.30 (2H, d, J=8.2 Hz, 2×ArH), 7.31 (1H, d, J=1.5 Hz, 5′-H), 7.80 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 20.2 (Me), 20.6 (Me), 21.4 (Me), 21.6 (ArMe), 59.9 (5-CH), 60.9 (2-CH), 63.4 (CH_2OAc), 71.7 (3-CH), 73.2 (4-CH), 119.6 (3′-CH), 110.5 (4′-CH), 127.9 (CH), 129.5 (CH), 134.3 (C), 142.9 (5′-CH), 143.9 (C), 149.5 (C), 169.2 (C═O), 169.3 (C═O), 170.3 (C═O); m/z (APCI) found: M^++1 (100%), 480.1329. $C_{22}H_{26}NO_9S$ requires: M, 480.1328.

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References and notes

1. Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS: Philadelphia, PA, 1984; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986; Liotta, D. *Organoselenium Chemistry*; Wiley Interscience: New York, NY, 1987.
2. Wirth, T. *Tetrahedron* **1999**, *55*, 1; Tiecco, M. Electrophilic Selenium, Selenocyclisations. In *Organoselenium Synthesis: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Topics in Current Chemistry; Springer: Heidelberg, 2000; p 7; Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3740.
3. For recent examples, see: Lescop, C.; Mévellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187; Davies, H. M. L.; Cao, G. *Tetrahedron Lett.* **1998**, *39*, 5943.
4. See for example: Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887; Díaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501; Kassou, M.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 3696; Costenaro, E. R.; Fontoura, L. A. M.; Oliveira, D. F.; Correia, C. R. D. *Tetrahedron Lett.* **2001**, *42*, 1599.
5. Tingoli, M.; Tiecco, M.; Testaferri, L.; Andrenacci, R.; Balducci, R. *J. Org. Chem.* **1993**, *58*, 6097.
6. Danishefsky, S.; Regan, J.; Doehner, R. *J. Org. Chem.* **1981**, *46*, 5255; Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379; Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393; Li, B.; Smith, M. B. *Synth. Commun.* **1995**, *25*, 1265; Bailey, J. H.; Cherry, D. T.; Crapnell, K. M.; Moloney, M. G.; Shim, S. B. *Tetrahedron* **1997**, *53*, 11731 and references cited therein.
7. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
8. Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217.
9. Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287 and reference cited therein.

10. See, for example, Rüeger, H.; Benn, M. H. *Can. J. Chem.* **1982**, *60*, 2918; Tsai, Y.-M.; Ke, B.-W.; Yang, C.-T.; Lin, C.-H. *Tetrahedron Lett.* **1992**, *33*, 7895; Baldwin, J. E.; Field, R. A.; Lawrence, C. C.; Lee, V.; Robinson, J. K.; Schofield, C. J. *Tetrahedron Lett.* **1994**, *35*, 4649; Mater, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullié, M. M. *J. Org. Chem.* **1994**, *59*, 5192; Lin, C.-C.; Shimazaki, M.; Heck, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzen, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826; Robinson, J. K.; Lee, V.; Claridge, T. D. W.; Baldwin, J. E.; Schofield, C. J. *Tetrahedron* **1998**, *54*, 981; Greenwood, E. S.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **2003**, *59*, 3307; Curtis, K. L.; Fawcett, J.; Handa, S. *Tetrahedron Lett.* **2005**, *46*, 5297.
11. Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329; Mans, D. M.; Pearson, W. H. *J. Org. Chem.* **2004**, *69*, 6419.
12. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858; For cyclisations which favour a 6-*exo* pathway over 5-*endo* processes in alkenyl carbamates, see: Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724.
13. Clive, D. L.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120; Clive, D. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 379; For similar cyclisations but using *N*-phenylselenosuccinimide, see: Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704; Webb, R. R.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357; Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429; For an elegant combination of selenocyclisation followed by *N*-alkylation to establish the pyrrolizidine system in mitomycin, see: Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891; See also: Back, T. G.; Dyer, B. P.; Nan, S. *Tetrahedron* **1999**, *55*, 3191 (carbamate cyclisations); Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1837 (*N*-alkenyl imidate cyclisations).
14. Berthe, B.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393.
15. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1493; See also: Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660; Takada, H.; Nishibayashi, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1511; Fragale, G.; Wirth, T. *Eur. J. Org. Chem.* **1998**, 1361.
16. Boelens, M.; DeKimpe, N. *J. Chem. Soc., Chem. Commun.* **1993**, 916; De Smaele, D.; De Kimpe, N. *J. Chem. Soc., Chem. Commun.* **1995**, 2029.
17. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L. *J. Chem. Soc., Chem. Commun.* **1995**, 235; Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Chem. Soc., Chem. Commun.* **1995**, 237; Tiecco, M.; Testaferri, L.; Marini, F. *Tetrahedron* **1996**, *52*, 11841; Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F.; Santi, C.; Temperini, A. *Gazz. Chim. Ital.* **1996**, *126*, 635; Tiecco, M.; Testaferri, L.; Tingoli, M.; Santi, C. *Tetrahedron Lett.* **1995**, *36*, 163; Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Santi, C. *Tetrahedron* **1995**, *51*, 1277; Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3053.
18. Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218 and references therein; For applications, see: Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143; Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. D. *J. Am. Chem. Soc.* **1999**, *121*, 11963; Ley, S. V.; Cleator, E.; Hewitt, P. R. *Org. Biomol. Chem.* **2003**, *1*, 3492; Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2415; For the generation of oxygen analogues, see: Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2005**, *7*, 941.
19. Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182.
20. For a review, see: Knight, D. W. *Prog. Heterocycl. Chem.* **2002**, *14*, 19.
21. For a preliminary report of some of these results, see: Jones, A. D.; Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267.
22. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 361.
23. Evans, A. B.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 6947.
24. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
25. Raederstorff, D.; Shu, A. Y. L.; Thompson, J. E.; Djerassi, C. *J. Org. Chem.* **1987**, *52*, 2337.
26. Williams, D. R.; White, F. W. *J. Org. Chem.* **1987**, *52*, 5067.
27. Stork, G.; Leong, A. Y. M.; Touzin, A.-M. *J. Org. Chem.* **1976**, *41*, 3491.
28. Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874.
29. Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1998**, *39*, 8909.