Novel asymmetric phenylselenium-induced lactamizations of olefinic amides: stereoselective routes to α- and β-amino acids

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Organoselenium-induced cyclofunctionalization of the (*S*)-*N*-(α,β-unsaturated) acylprolinamides 1, 7 and 14 has been found to produce the 7-membered bislactam products 2 and 15, or the 6-membered phenylselenolactam products 8 and 9 depending on the substitution pattern of the enone moiety of the starting material. The structural identities and stereochemistry of the cyclized products have been determined by X-ray diffraction, and the diastereoselectivity in the formation of the 7-membered ring bislactam product was found to be 91.6% de. The mechanism of the cyclolactamization is discussed.

Introduction

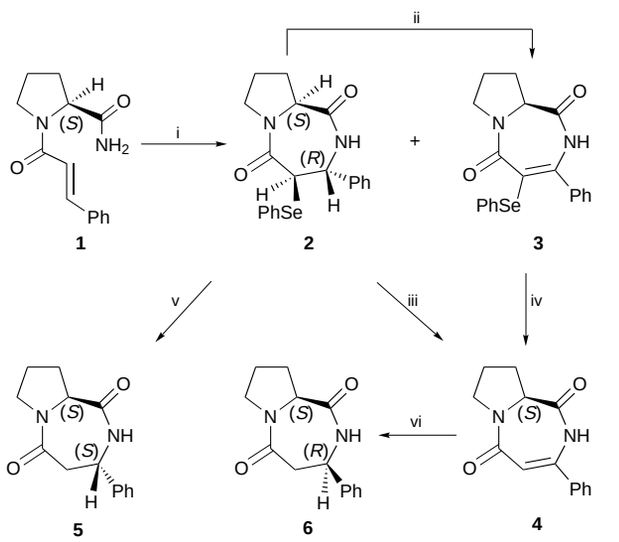
Electrophilic heteroatom cyclizations of olefinic compounds leading to a variety of 5- and 6-membered ring heterocycles have been extensively investigated. For example, halogenolactonization of alkenes with an intramolecular carboxylate nucleophile and various cyclofuntionalizations of olefins with internal hydroxy, amino, sulfur and phosphorus functional groups are well-studied.[1] The successful application of these methods to the synthesis of specific target molecules requires appropriate combinations of substrate geometry,[2] nucleophilic functionality and the activating electrophile, the most frequently used electrophiles being halogenium, Hg^{II} and phenylselenium ions.[3]

In the cyclofunctionalization of olefinic amides promoted by a number of electrophiles, the predominant product is usually not the lactam, but the imino ether which subsequently hydrolyses to the corresponding lactone, *i.e.* the oxygen atom instead of the nitrogen in the amide functionality preferentially attacks the developing electrophilic centre.[3c,4] The only reported exceptions include halogenocyclization of *N*-sulfonyl, *N*-butyl, *N*-isoxazolyl and *N*-thiazoyl olefinic amides.[5] In order to cyclofunctionalize olefinic amides to lactams, it is normally necessary to utilize the protected forms of amide functionality such as bis-silylated imidate, thioimidate and *O*-acylhydroxamate.[6] We have studied the asymmetric version of the organoselenium-induced cyclization of olefinic amides as a potential route to chiral α- or β-amino acids, and here report novel lactamizations with high degrees of chirality transfer.[7]

Results and discussion

The required substrate, (*S*)-*N*-cinnamoylprolinamide **1** was efficiently prepared from (*S*)-proline by successive reactions with (i) cinnamoyl chloride and NaOH in aqueous acetone at 0 °C, (ii) methyl chloroformate and triethylamine and (iii) ammonium hydroxide at −10 °C. After considerable experimentation with a number of electrophiles under a variety of reaction conditions, benzeneselenenyl bromide (PhSeBr), silver triflate (AgOTf)[8] and DMF in Me_3CN was found to be most suitable for the desired cyclofunctionalization of **1** (Scheme 1).

Thus, treatment of compound **1** with PhSeBr (3 mol equiv.), AgOTf (3 mol equiv.) and DMF (20–30 mol equiv.) in dry Me_3CN at room temperature under Ar, gave a mixture of the cyclic products **2** and **3** in a varying ratio depending on the reaction time (Table 1). For instance, after 12 h compound **2** was isolated in 31% yield together with the starting material **1** (65%), whereas after 48 h products **2** (5%) and **3** (72%) were obtained along with a trace amount of **1** (runs 1–3). It could be



Scheme 1 Cyclofunctionalization of **1** and subsequent conversions to (L)-and (D)-β-AA derivatives. *Reagents*: i, PhSeBr, AgOTf, DMF, CH_3CN; ii, PhSeBr, AgOTf, DMF, CH_3CN, 70%; iii, H_2O_2 (30%), THF, 77%; iv, $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF, MeOH, 88%; v, $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF, MeOH, 87% (**5**:**6** = 22.8:1); vi, Pd–C, H_2, MeOH, 89% (**5**:**6** = 1:4.56).

shown that the initial product was **2** by converting the isolated pure product **2** into product **3** in 70% yield under identical reaction conditions, or in *ca*. 30% yield upon treatment with PhSeBr in DMF and Me_3CN (runs 5 and 7). It was also found that the reaction of **1** with PhSeBr (1.8 equiv.), AgOTf (2 equiv.) and DMF (20 equiv.) in dry Me_3CN at room temperature under Ar for 12 h gave almost exclusively product **2** (73% isolated yield) together with trace amounts of **1** and **3** (run 4). It is to be emphasized that without DMF, the cyclization reaction rarely proceeded, but the role of DMF has yet to be clarified. Addition of NaH instead of DMF to the reaction mixture gave a mixture of **2** and **4** (run 6).

The products **2** and **3** showed similar polarities on a TLC plate, but the UV spectra indicated a distinct difference between them. While the UV spectrum of **2** shows only bands at 224 (ε, 3311, *E*-band of Ph) and 266 nm (ε, 712, *B*-band of Ph), the spectrum of **3** contains a main band at 210 nm (ε, 7875, *E*-band of Ph), whose intensity and position vary with the degree of coplanarity and conjugation of double bond in addition to the characteristic subsidiary maxima at 258 (ε, 4170, $\pi \longrightarrow \pi^*$; *K*-band) and 320 nm (ε, 1453, $n \longrightarrow \pi^*$; *R*-band). The ^1H NMR spectrum of **2** displayed three 1H signals at 4.71 [d,

Table 1 Phenylselenolactamization

		Conditions[a]				Products (%)[b]			
Run	Substrate	PhSeBr (equiv.)	AgOTf (equiv.)	DMF (equiv.)	Time (h)	**1**	**2**	**3**	**4**
1	**1**	3	3	30	12	65	31	—	—
2	**1**	3	3	30	24	38	—	57	—
3	**1**	3	3	20	48	ND[c]	5	72	—
4	**1**	1.8	2	20	12	ND[c]	73	Trace	—
5	**2**	3.3	3	20	48	—	—	70	—
6	**1**	1.8	2	1.2[d]	12	ND[c]	30	—	34
7	**2**	3	—	30	48	—	6	29	6

[a] All reactions were carried out in dry acetonitrile under argon at room temperature. [b] Isolated yield by column chromatographt on SiO_2. [c] Identified by TLC but not determined. [d] NaH was used instead of DMF; runs with NaH, SiO_2, PhSeBr, AgOTf in CH_2Cl_2 at 0 °C gave similar results.

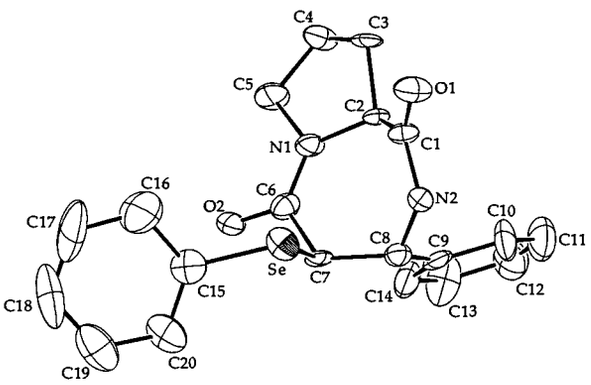


Fig. 1 X-Ray crystal structure of compound **2**

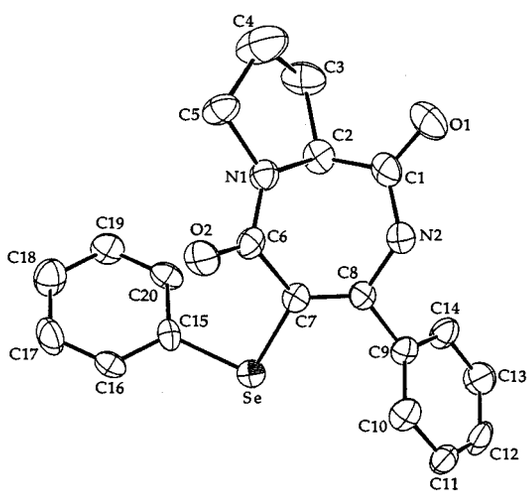


Fig. 2 X-Ray crystal structure of compound **3**

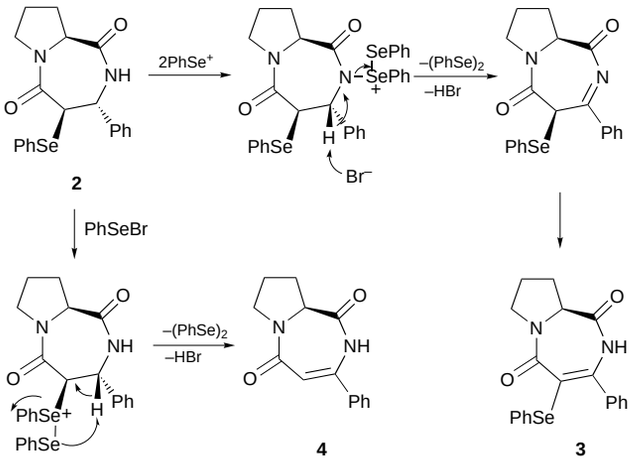
J 8.7 Hz, 1H, C(O)C*H*SePh], 4.82 (dd, *J* 8.7, 4.4 Hz, 1H, NHC*H*Ph) and 6.24 (d, *J* 4.4 Hz, 1H, NH), thus revealing the connectivity pattern of the structure. However, a more definitive structural elucidation together with stereochemical assignments for the products **2** and **3** were made on the basis of single-crystal X-ray diffraction studies (Figs. 1 and 2). It is clear from the X-ray structure of **2** that the amide nitrogen has attacked the β-position of the cinnamoylamide moiety thus generating a 7-membered system, and that the electrophile-promoted addition occurs in an *anti* fashion with an *R*-absolute configuration at the new chiral centre of C*-NH. However, the reason for the exclusive formation of the lactam product as opposed to the usual lactone *via* imino ether species is not at present clear, although it is currently speculated that the hard/soft-ness of the effective electrophiles and the transition state geometry may be playing important roles.

The crude product **2** was deselenenylated in 87% yield with nickel boride generated *in situ* from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ in THF–MeOH[9] to give compound **5**. An HPLC analysis of the crude product **5** (Alltech RP-18; 4.6 × 250 mm; 25% Me_3CN in water; 1.5 ml min^{-1}; detection at 208 nm) indicated that the diastereoisomeric ratio at this stage was *ca.* 22.8 : 1, equivalent to *ca.* 91.6% de. Similarly, compound **3** was deselenenylated to **4** in 88% yield by the nickel boride procedure. Alternatively, the oxidative elimination of compound **2** with H_2O_2 (30%) in THF[10] was carried out in 77% yield to provide **4**, which was hydrogenated over Pd–C in MeOH to give a diastereoisomeric mixture of **5** and **6** in the ratio of 1 : 4.56 (% de = 64.0) on the basis of HPLC analysis. It is noteworthy that in the catalytic hydrogenation of both compound **4** and the exocyclic double bond in the diketopiperazine derivatives,[11] derived from (*S*)-proline and α-keto acids, the catalyst-bound hydrogen approaches from the convex side of the molecules, *i.e.* the same side as the chiral hydrogen of the (*S*)-proline auxiliary, although the 1,4 chirality transfer efficiency appears to be slightly higher in the 6-membered ring than in the 7-membered ring (**4**).

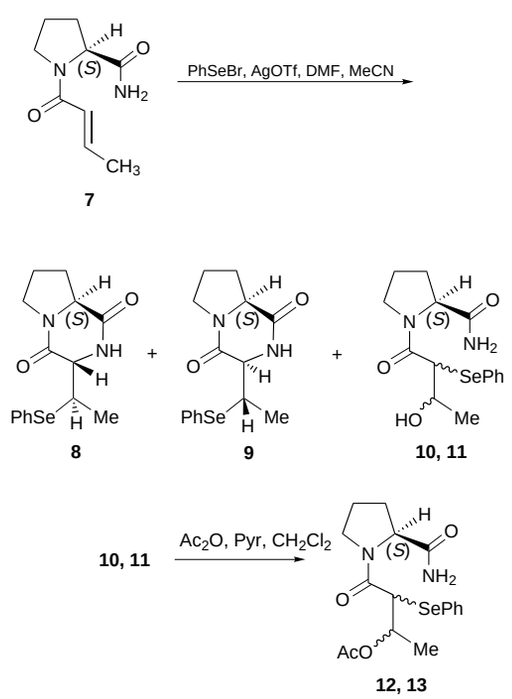
In its UV spectrum, **4** as a solution in MeOH showed λ_m at 206 (ε 15 739, *E*-band of Ph), 228 (ε, 14 768, *B*-band of cinnamoyl moiety) and 278 nm (ε, 9990, *K*-band of cinnamoyl moiety), whereas the diastereoisomeric pair **5** and **6** showed only the *E*-band at 208 nm (ε, 3311) because of destruction of the conjugated system. The ^{1}H NMR chemical shifts of **5** were assigned on the basis of ^{1}H-^{1}H homonuclear correlation spectroscopy (COSY). The ^{1}H NMR signals appear at δ 2.76, 3.20 [C(O)CH_2] and 4.82 (CHPh) for compound **5**, and at δ 2.95, 3.14 [C(O)CH_2] and 4.94 (CHPh) for compound **6**. The specific optical rotations of **5** and **6** were −92.40 and 8.54, respectively, whilst other spectroscopic features (high resolution mass, UV and IR) were very similar.

The conversion of compound **2** into **3** represents an overall *trans* dehydrogenation, and might be occurring through the initial *N*-phenylselenation followed by the elimination of a 'phenylselenol equivalent' to give an imine, which isomerizes to **3** (Scheme 2). Similarly, the production of **4** from compound **2** might be explicable in terms of the diphenyldiselenium species and an intramolecular elimination (see Scheme 2).

When another substrate, (*S*)-*N*-crotonoylprolinamide **7**, prepared from (*S*)-proline and crotonyl chloride, was subjected to the phenylselenium-induced lactamization under the similar conditions, *i.e.* PhSeBr (1.8 equiv.), AgOTf (2 equiv.) and DMF (20 equiv.) in dry Me_3CN, somewhat different results were obtained (Scheme 3). While the lactamization of **7** was found to be very sluggish and gave the 6-membered diketopiperazine compounds **8** (13.2%) and **9** (4.2%), the simple addition of phenylselenium ion to the olefinic moiety of **7** followed by trapping with water gave a predominance of apparently diastereoisomeric products **10** (46%) and **11** (19.4%). The structures of the 6-membered bislactam diastereoisomers (**8** and **9**) were again ascertained by single-crystal crystallography (Figs. 3 and 4). Despite the low yields, formation of the 6-membered diketopiperazine products **8** and **9** was observed for the first time in this phenylselenolactamization. Compounds **8** and **9**, in principle,



Scheme 2 A proposed mechanism for the conversion of **2** into **3** and **4**



Scheme 3 Cyclofunctionalization of **7**

could be used as precursors of the unnatural α-(*R*)-amino acid and α-(*S*)-amino acid, respectively. The simple PhSe-added diastereoisomers incorporated the hydroxy group as nucleophile, perhaps most likely due to the hydrolysis during the aq. $NaHCO_3$ work-up, after the initial trapping of the carbocationic intermediates with the trifluoromethanesulfonate anion. The presence of the secondary hydroxy groups in **10** and **11** could be confirmed by analysing the ^{1}H NMR spectra of the acetylated compounds **12** and **13**. Large chemical-shift changes for the C*H*CH_3 signals in ^{1}H NMR spectra (>+1 ppm) between the starting materials (**10** and **11**) and the products (**12** and **13**) indicate that the hydroxy group is bonded to the *C*HCH_3 moiety.

Next, the cyclofunctionalization of (*S*)-*N*-(β-methylcrotonyl)-prolinamide **14** was examined under similar reaction conditions. In this case, the only cyclized product was found to be the 7-membered lactam **15** (22.4%). In addition, two apparent diastereoisomeric PhSe-added alcohols **16** (49%) and **17** (13.3%) were obtained again as the simple electrophilic addition products (Scheme 4). In order to elucidate the structure of **15**, the reductive deselenenylation was carried under the same conditions as described above ($NiCl_2$·$6H_2O$ and $NaBH_4$ in THF–

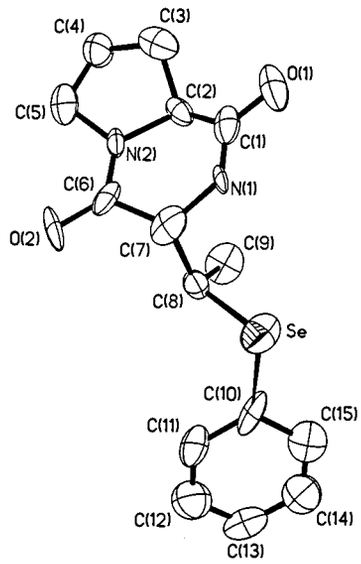


Fig. 3 X-Ray crystal structure of compound **8**

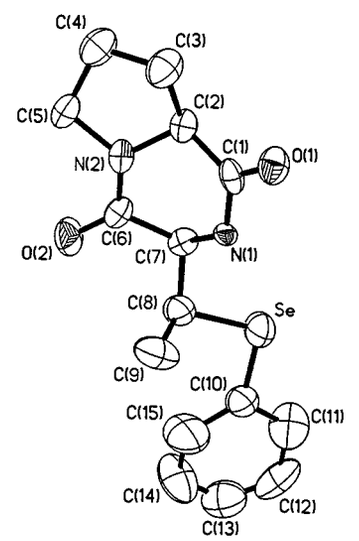
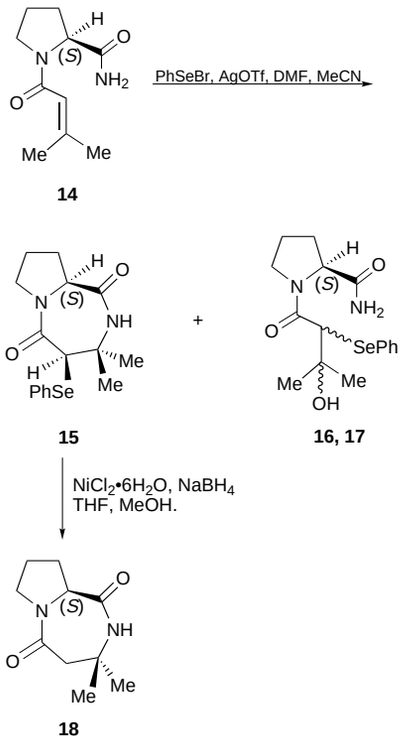


Fig. 4 X-Ray crystal structure of compound **9**

MeOH). The 7-membered ring structure was clearly indicated by the ^{1}H NMR spectrum of deselenenylated product **18**, which exhibited two isolated methyl groups and two diastereotopic protons at 2.47 and 3.07 ppm with the geminal coupling *J* 14.1 Hz).

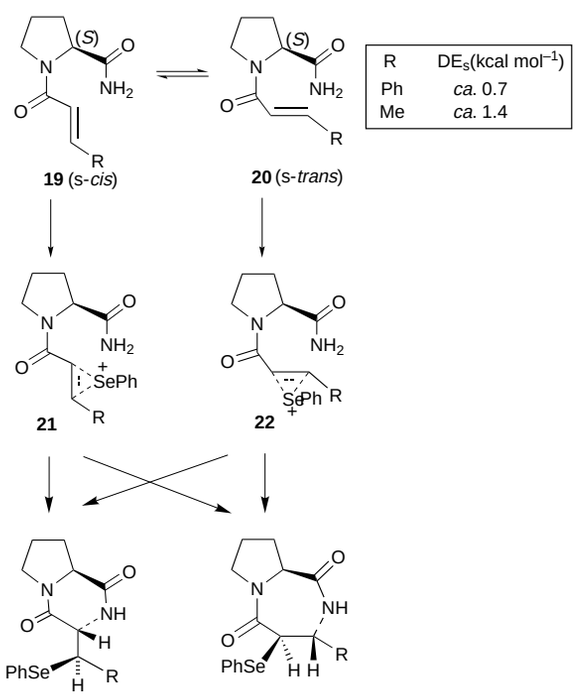
That the phenylselenolactamization of **1** and **14** afforded the 7-membered bislactam product **2** and **15**, whereas the lactamization of **7** gave the 6-membered diketopiperazines **8** and **9**, clearly suggest that the electronic factors around the double bond and the geometry of the initial intermediates generated by addition of the phenylselenium ion to the double bond may play important roles. Comparison of the reaction rates, chemical yields and the product structures observed in the above cyclofunctionalizations also suggest that compound **1** shows a higher reactivity towards the phenylselenium electrophile than do **7** and **14**. The fact that (monoaryl- or dialkyl-substituted α,β-unsaturated)acylprolines **1** and **14** gave the 7-membered ring products **2** and **15**, while (monoalkyl substituted α,β-unsaturated)acylproline **7** afforded the 6-membered phenylselenolactams **8** and **9** suggest that an effective cation-stabilizing substituent at the β-position is needed for the formation of the 7-membered ring. Otherwise, the formation of a 6-membered ring product is favoured, although the overall reaction rate is rather low. In this connection it is interesting to note the α-substituent effect on the mode of the cyclization. A prelimin-



Scheme 4 Cyclofunctionalization of **14**

ary experiment with *N*-(2-methylpent-2-enoyl)prolinamide showed that the 6-membered ring products were preferentially formed in the cyclofunctionalization. This reaction could provide a convenient synthetic route to α,α-disubstituted α-amino acids.[12]

According to the PM3 calculations, the s-*cis* structure **19** is more stable than s-*trans* **20** by *ca.* 0.7–1.4 kcal mol^{-1} (Scheme 5). Thus, the presumed bridged phenylselenium ion inter-



Scheme 5 Mode of cyclofunctionalization

mediates generated *en route* to the formation of bislactams might actually be an equilibrium mixture of the two geometrically different types (**21** and **22**). In the subsequent asymmetric cyclofunctionalizations, the bridged phenylselenium ions (**21** and **22**) are attacked regioselectively at the α or β position by the internal carboxamide nucleophile in an S_N2 or S_N1 fashion. In the direct S_N2 type cyclization, both 6-*exo*-*trig* and 7-*endo*-*trig* modes would be expected to be possible.[2]

In summary, it has been demonstrated that the cyclofunctionalization (*S*)-*N*-(α,β-unsaturated)acylprolinamides should provide an efficient route to both (*S*)- and (*R*)-β-amino acids,[13] since the diastereoisomeric cyclic dipeptides such as **5** and **6** can be easily purified and hydrolysed to the corresponding chiral β-amino acids and the chiral auxiliary which can be recycled.[11c] In spite of the low chemical yields, the possibility that (*S*)- and (*R*)-α-amino acids could also be synthesized by the cyclofunctionalization has been shown in the cases where the substrate includes an electron-deficient olefin moiety. A study to define the generality and scope of this cyclolactamization route and the possible control of the cyclization mode is currently in progress.

Experimental

General

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained on a BOMEM model FT-IR M100-C15 spectrometer for liquid films. Optical rotations, recorded as 10^{-1} deg cm^2 g^{-1}, were measured on a JASCO DIP-360 digital polarimeter at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g 100 ml^{-1}, solvent). NMR spectra were determined on a Bruker AM 300 (300 MHz) spectrometer. Chemical shifts are reported in δ ppm relative to $SiMe_4$ for ^{1}H and ^{13}C NMR spectra. Coupling constants, *J* are reported in Hz. NMR multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Assignments of ^{1}H resonances were assisted by COSY spectral data. Elemental analyses were performed by Galbraith laboratories, Inc., Knoxville, TN, USA. Mass spectra were determined on a KRATOS MS 25 RFA (EI and FAB) system. High resolution MS were performed by Korea Basic Science Center, Taejeon, Korea. Selenium-containing compounds exhibited the characteristic isotopic family in their mass spectra [^{74}Se(1), ^{76}Se(10), ^{77}Se(9), ^{78}Se(27), ^{80}Se(57), ^{82}Se(11)] but only the peaks due to the most abundant isotope (^{80}Se) are reported.

Analytical thin-layer chromatography was performed on Merck 60 F_{254} silica gel plate (0.25 mm layer thickness) and visualization was done with UV light, and/or a spray with 5% phosphomolybdic acid in ethanol followed by charring with a heat gun. Column chromatography was carried out on silica gel 60 (E. Merck, 70–230 mesh). HPLC was performed on RP 18 Alltech column (250 × 4.6 mm) using an SP 8800 ternary pump and SP 8450 UV/Vis detector (λ = 208 nm). Relative peak areas were determined by an SP 4290 integrator.

All reactions were carried out under the argon atmosphere in oven-dried glassware, all commercial chemicals were used as obtained and all solvents were carefully dried and distilled by standard methods prior to use. DMF was dried by storage over $MgSO_4$ and vacuum distilled. Dichloromethane and acetonitrile were dried and distilled over P_2O_5.

(*S*)-*N*-Cinnamolyprolinamide 1

A solution of (*S*)-proline (5.0 g, 43 mmol) in 2 M aqueous NaOH (26 ml, 52 mmol) was cooled in an ice-bath and diluted with acetone (26 ml). An acetone solution (26 ml) of cinnamoyl chloride (8.0 g, 48 mmol) and 2 M aqueous NaOH (30 ml, 61 mmol) were simultaneously added over 40 min with good stirring to the aqueous proline in an ice-bath. After 3 h at room temperature, the mixture was evaporated *in vacuo* to remove the acetone. The residual solution was washed with ether and acidified (pH 2) with conc. hydrochloric acid. The acidic mixture, after saturation with NaCl, was extracted with ethyl acetate, and the combined extracts were washed with brine and evaporated. Recrystallization of the crude product from methanol gave pure (*S*)-cinnamoylproline (8.7 g, 82%).

To a solution of (*S*)-cinnamoylproline (6.4 g, 26 mmol) and triethylamine (3.7 ml, 26 mmol) in CH_2Cl_2 (120 ml) at −20 °C, methyl chloroformate (2.0 ml, 26 mmol) was added dropwise. After the mixture had been stored for 1 h at −20 °C, 30% aqueous NH_4OH (25 ml, excess) was added to it dropwise. Stirring was continued for 2 h at room temperature by which time evolution of CO_2 had subsided. The mixture was concentrated and neutralized (pH 7) with 1 M hydrochloric acid. The residual solution was extracted with CH_2Cl_2, and the extract was dried and evaporated to give a crude product, which was recrystallized from MeOH–hexane. Compound **1** (5.4 g, 85%), mp 175–178 °C; $[\alpha]_D$ −218.0 (*c* 1.1, $CHCl_3$); R_F 0.1 (silica, ethyl acetate); λ_{max}(MeOH)/nm 208, 220 and 282; ν_{max}(film)/cm^{-1} 3320, 2935, 1680, 1648, 1597, 1454, 1422 and 759; δ_H($CDCl_3$) 1.80–2.10 (m, 3H, C*H*C*H*$_2$CH$_2$N), 2.52 (m, 1H, C*H*CH$_2$CH$_2$N), 3.72 (m, 2H, C*H*$_2$N), 4.76 (br d, *J* 8.1, 1H, C*H*CH$_2$CH$_2$CH$_2$N), 6.75 (d, *J* 15.6, 1H, C*H*Ph), 7.37–7.55 (m, 5H, Ph) and 7.75 [d, *J* 15.6, 1H, C(O)CH]; δ_C($CDCl_3$) 25.56, 27.65, 48.11, 60.30, 118.41, 128.61, 129.48, 130.61, 135.50, 144.03, 166.83 and 174.11; *m*/*z* (EI) 244 (M^+).

(3*R*,4*R*,9a*S*)-3-Phenyl-4-phenylselenooctahydropyrrolo[1,2-*a*]-[1,4]diazepine-1,5-dione 2

To a solution of cinnamoylprolinamide **1** (200 mg, 0.82 mmol) in acetonitrile (7 ml) were added silver trifluoromethanesulfonate (420 mg, 1.64 mmol) in acetonitrile (8 ml), and then benzeneselenyl bromide (384 mg, 1.47 mmol) and dimethylformamide (1.30 ml, 16.4 mmol) in acetonitrile (8 ml). The resulting solution was stirred at ambient temperature for 12 h after which it was treated with saturated aqueous $NaHCO_3$ and extracted with methylene dichloride. The extract was washed with brine, dried and evaporated to give the crude product. Column chromatography of this afforded **2** (240.0 mg, 73.4%) as a white solid, recrystallization of which from CH_2Cl_2–hexane gave colourless crystals, mp 194–195 °C; $[\alpha]_D$ +26.66 (*c* 1.015, $CHCl_3$); R_F 0.51 (silica, ethyl acetate); λ_{max}(MeOH)/nm 224 and 266; ν_{max}(film)/cm^{-1} 3140, 1683, 1652, 1432 and 749; δ_H($CDCl_3$) m, 2H, C*H*$_2$CH$_2$N), 2.03 (m, 1H, C*H*CH$_2$CH$_2$N), 2.59 (m, 1H, C*H*CH$_2$CH$_2$N), 3.60 (m, 2H, CH$_2$N), 4.19 (dd, *J* 7.5, 6.2, 1H, C*H*CH$_2$CH$_2$CH$_2$N), 4.71 [d, *J* 8.7, 1H, C(O)C*H*SePh], 4.82 (dd, *J* 8.7, 4.4, 1H, NHC*H*Ph), 6.24 (d, *J* 4.4, 1H, NH) and 7.07–7.32 (m, 10H, Ph); δ_C($CDCl_3$) 23.08, 29.29, 48.46, 52.40, 59.92, 60.95, 127.53, 128.55, 129.04, 129.33, 129.49, 135.59, 139.68, 168.97 and 170.77; *m*/*z* (EI) 400 (M^+) (Found C, 60.16; H, 5.07; N, 7.05. Calc. for $C_{20}H_{20}N_2O_2Se$: C, 60.15; H, 5.05; N, 7.02%).

(9a*S*)-3-Phenyl-4-phenylseleno-1,2,7,8,9,9a-hexahydro-5*H*-pyrrolo[1,2-*a*][1,4]diazepine-1,5-dione 3

(A) To a solution of cinnamoylprolinamide **1** (150 mg, 0.61 mmol) in acetonitrile (6 ml) were added silver trifluoromethanesulfonate (474 mg, 1.84 mmol) in acetonitrile (8 ml), and benzeneselenyl bromide (435 mg, 1.84 mmol) and dimethylformamide (0.95 ml, 12.3 mmol) in acetonitrile (8 ml). The resulting mixture was stirred at ambient temperature for 48 h after which it was treated with saturated aqueous $NaHCO_3$, and extracted with methylene dichloride. The extract was washed with brine, dried and evaporated to give the crude product. Column chromatography of this afforded **2** (12.4 mg, 5.1%) and **3** (175.2 mg, 71.6%) as white solids, which were recrystallized from CH_2Cl_2–hexane.

(B) To a solution of **2** (160.0 mg, 0.040 mmol) in acetonitrile (1 ml) were added silver trifluoromethanesulfonate (30.8 mg, 0.12 mmol) in acetonitrile (1 ml) and benzeneselenyl bromide (31.3 mg, 0.13 mmol) and dimethylformamide (0.093 ml, 1.2 mmol) in acetonitrile (2 ml). The resulting mixture was stirred at ambient temperature for 48 h after which it was treated with saturated aqueous $NaHCO_3$ and extracted with methylene dichloride. The extract was washed with brine, dried and evaporated to give the crude product, column chromatography of which afforded **3** (11.2 mg, 70.4%) as a white solid, mp 215–216 °C; $[\alpha]_D$ +178.39 (*c* 1.05, $CHCl_3$); R_F 0.50 (silica, ethyl acetate); λ_{max}(MeOH)/nm 210, 258 and 320; ν_{max}(film)/cm^{-1} 3230, 1895, 1821, 1420 and 751; δ_H($CDCl_3$) 1.86–2.12 (m, 3H, C*H*C*H*$_2$CH$_2$N), 2.71 (m, 1H, C*H*CH$_2$CH$_2$N), 3.26 (dt, *J* 11.8, 8.1, 1H, CH$_2$N), 3.66 (m, 1H, CH$_2$N), 4.25 (dd, *J* 7.5, 2.6, 1H, C*H*CH$_2$CH$_2$CH$_2$N) and 7.11–7.42 (m, 10H, Ph); δ_C($CDCl_3$) 23.86, 26.51, 47.31, 58.04, 117.41, 128.22, 129.33, 129.52, 129.61, 130.90, 131.86, 134.04, 137.59, 142.07, 168.97 and 170.77; *m*/*z* (EI) 398 (M^+); (FAB) 421 (M + 23) and 399 (M + 1).

(9a*S*)-3-Phenyl-1,2,7,8,9a-hexahydro-5*H*-pyrrolo[1,2-*a*][1,4]-diazepine-1,5-dione 4

(A) To a solution of **2** (60 mg, 0.15 mmol) in THF (3 ml) at 0 °C was added dropwise 30% aqueous H_2O_2 (0.1 ml), and the resulting mixture was stirred at 20 °C for 2 h. It was then diluted with water (2 ml) and extracted with CH_2Cl_2. The combined extracts were washed with 10% aqueous Na_2CO_3, dried and concentrated. Column chromatography of the residue afforded **4** (28.1 mg, 77.2%) as a white solid.

(B) To a solution of **3** (146 mg, 0.367 mmol) in THF (5 ml) was added a solution of nickel(II) chloride hexahydrate (349 mg, 1.47 mmol) in MeOH (5 ml) at ambient temperature. The solution was cooled in an ice-bath and treated with sodium borohydride (167 mg, 4.41 mmol), added in small portions. After an additional 10 min at 0 °C, the mixture was filtered through Celite and chromatographed to give **4** (78.7 mg, 88.3%) as a white solid, mp 187–188 °C; $[\alpha]_D$ +326.88 (*c* 1.00, $CHCl_3$); R_F 0.28 (silica, ethyl acetate); λ_{max}(MeOH)/nm 206, 228 and 278; ν_{max}(film)/cm^{-1} 3221, 1700, 1634, 1599, 1440 and 761; δ_H($CDCl_3$) 1.88–2.10 (m, 3H, C*H*C*H*$_2$CH$_2$N), 2.76 (m, 1H, C*H*CH$_2$CH$_2$N), 3.61 (m, 2H, CH$_2$N), 4.27 (dd, *J* 8.1, 2.5, 1H, C*H*CH$_2$CH$_2$CH$_2$N), 6.04 (d, *J* 1.2, 1 H, C*H*Ph) and 7.26–7.55 (m, 5H, Ph); δ_C($CDCl_3$) 24.13, 26.64, 47.30, 58.26, 110.22, 127.63, 129.75, 131.29, 136.62, 142.81, 166.77 and 170.11; *m*/*z* (EI) 242 (M^+).

(3*S*,9a*S*)-3-Phenyloctahydropyrrolo[1,2-*a*][1,4]diazepine-1,5-dione 5

To a solution of **2** (71.6 mg, 0.18 mmol) in THF (3 ml) was added a solution of nickel(II) chloride hexahydrate (85.2 mg, 0.36 mmol) in MeOH (3 ml) at ambient temperature. The solution was cooled in an ice-bath and treated with sodium borohydride (40.74 mg, 1.07 mmol), added in small portions. After an additional 10 min at 0 °C, the mixture was filtered through Celite and chromatographed to give a crude solid product **5** (38.2 mg, 87.2%). HPLC analysis indicated the ratio of **5** and **6** to be 22.8 : 1. Recrystallization of the crude product from ethyl acetate–hexane gave colourless crystalline **5**, mp 154–155 °C; $[\alpha]_D$ −92.40 (*c* 0.610, $CHCl_3$); R_F 0.26 (silica, ethyl acetate); λ_{max}(MeOH)/nm 210 and 286; ν_{max}(film)/cm^{-1} 3246, 1649, 1453 and 759; δ_H(300 MHz, $CDCl_3$) 1.80 (m, 2H, C*H*$_2$CH$_2$N), 2.18 (m, 1H, C*H*CH$_2$CH$_2$N), 2.76 (m, 2H, C*H*CH$_2$CH$_2$N + C(O)C*H*$_2$), 3.20 [app.t, *J* 13.3, 1H, C(O)C*H*$_2$], 3.58 (t, *J* 6.8, 2H, C*H*$_2$N), 4.59 (dd, *J* 8.1, 4.4, 1H, C*H*CH$_2$CH$_2$CH$_2$N), 4.82 (dd, *J* 13.3, 1.5, 1H, C*H*Ph), 5.83 (s, 1H, N*H*) and 7.26–7.41 (m, 5H, Ph); δ_C($CDCl_3$) 23.98, 29.25, 44.30, 47.25, 57.36, 60.28, 126.38, 129.21, 129.87, 142.64, 169.43 and 170.62; *m*/*z* (EI) 244 (M^+) [Found (HRMS, EI): *m*/*z* 244.1216. Calc. for $C_{14}H_{16}O_2N_2$: 244.1212].

(3*R*,9a*S*)-3-Phenyloctahydropyrrolo[1,2-*a*][1,4]diazepine-1,5-dione 6

A mixture of Pd–C (10 mg) and **4** (20 mg, 0.083 mmol) in MeOH (1 ml) was stirred at ambient temperature under H_2 (1 atm) for 20 h, after which it was filtered and evaporated to give the crude product mixture (18.0 mg, 89.3%). This was found to contain **5** and **6** in a ratio of 1 : 4.56 by HPLC analysis. Repeated recrystallization of the crude product from ethyl acetate–hexane gave **6** as colourless crystals, mp 150–152 °C;

$[\alpha]_D$ −17.27 (*c* 0.75, $CHCl_3$); R_F 0.24 (silica, ethyl acetate); λ_{max}(MeOH)/nm 208 and 285; ν_{max}(film)/cm^{-1} 3244, 1646, 1447 and 755; δ_H($CDCl_3$) 1.88 (m, 2H, C$H_2$$CH_2N$), 2.15 (m, 1H, C*H*$CH_2CH_2N$), 2.70 (m, 1H, C*H*$CH_2CH_2N$), 2.95 [dd, *J* 16.5, 10.0, 1H, C(O)CH_2], 3.14 [dd, *J* 16.5, 3.7, 1H, C(O)CH_2], 3.61 (m, 2H, CH_2N), 4.62 (dd, *J* 7.5, 6.2, 1H, C*H*$CH_2CH_2CH_2N$), 4.94 (dt, *J* 10.0, 3.7, 1H, C*H*Ph), 6.09 (s, 1H, N*H*) and 7.26–7.43 (m, 5H, Ph); δ_C($CDCl_3$) 23.32, 29.16, 44.05, 48.46, 53.80, 58.42, 126.81, 129.45, 129.94, 139.81, 168.16 and 171.02; *m*/*z* (EI) 244 (M^+) [Found (HRMS, EI): *m*/*z* 244.1207. Calc. for $C_{14}H_{16}O_2N_2$: 244.1212].

(*S*)-*N*-Crotonylprolinamide 7

This compound was analogously prepared as described for **1**; mp 122–124 °C; $[\alpha]_D$ −274.63 (*c* 1.11, $CHCl_3$); R_F 0.1 (silica, ethyl acetate); ν_{max}(film)/cm^{-1} 3299, 3170, 1675, 1606, 1428, 965 and 753; δ_H($CDCl_3$) (dd, *J* 6.9, 1.9, 3H, CH_3), 1.97–2.08 (m, 3H, C*H*C$H_2$$CH_2N$), 2.37 (m, 1H, C*H*$CH_2CH_2N$), 3.60 (m, 2H, C$H_2$N), 4.64 (dd, *J* 8.0, 2.0, 1H, C*H*$CH_2CH_2CH_2N$), 6.16 (dd, *J* 15.0, 1.9, 1H, C*H*=$CHCH_3$) and 6.96 (dq, *J* 15.0, 6.9, 1H, CH=C*H*CH_3); δ_C($CDCl_3$) 17.84, 24.58, 27.59, 47.08, 59.30, 122.27, 142.18, 165.59 and 174.02; *m*/*z* (EI) 182 (M^+).

Cyclofunctionalization of (*S*)-*N*-crotonoylprolinamide 7

To a solution of (*S*)-*N*-crotonoylprolinamide **7** (725 mg, 4.0 mmol) in acetonitrile (50 ml) were added silver trifluoromethanesulfonate (3.37 g, 13.1 mmol) in acetonitrile (25 ml), and then benzeneselenyl bromide (2.82 g, 11.9 mmol) and dimethylformamide (9.2 ml, 119 mmol) in acetonitrile (25 ml). The resulting mixture was stirred at ambient temperature for 12 h after which it was treated with saturated aqueous $NaHCO_3$, and extracted with methylene dichloride. The organic layer was separated, washed with brine and evaporated to give the crude product. Column chromatography of this afforded **8** (178.4 mg, 13.2%) and **9** (56 mg, 4.2%) as colourless crystals and **10** (649 mg, 46.9%) and **11** (274.8 mg, 19.4%) as white solids.

(3*R*,9a*S*)-3-[(1′*R*)-1′-Phenylselenoethyl]-3-methyloctahydropyrrolo[1,2-*a*][1,4]diazepine-1,5-dione 8

Mp 110–111 °C; $[\alpha]_D$ −59.43 (*c* 0.655, $CHCl_3$); R_F 0.56 (silica, ethyl acetate); λ_{max}(MeOH)/nm 212 and 274; ν_{max}(film)/cm^{-1} 2935, 1756, 1673, 1458, 1373, 1194 and 742; δ_H($CDCl_3$) 1.60 (d, *J* 7.2, 3H, CH_3), 1.84 (m, 1H, C*H*CH_2N), 1.96–2.10 (m, 2H, C*H*CH_2CH_2N + C*H*CH_2N), 2.45 (m, 1H, C*H*CH_2CH_2N), 3.41 (ddd, *J* 11.8, 9.1, 2.6, 1H, CH*H*N), 3.59–3.70 (m, 2H, C*H*CH_3 + one of CH*H*N), 4.33 (dd, *J* 9.7, 6.7, 1H, C*H*CH_2-CH_2CH_2N), 4.89 [d, *J* 5.9, 1H, C(O)C*H*NH], 7.26–7.64 (m, 5H, Ph); δ_C($CDCl_3$) 18.95, 22.28, 30.35, 41.19, 45.88, 57.53, 84.94, 128.75, 129.64, 135.19, 135.57, 162.78 and 167.53.

(3*S*,9a*S*)-3-[(1′*S*)-1′-Phenylselenoethyl]-3-methyloctahydropyrrolo[1,2-*a*][1,4]diazepine-1,5-dione 9

Mp 139–140 °C; $[\alpha]_D$ −221.77 (*c* 0.82, $CHCl_3$); R_F 0.56 (silica, ethyl acetate); λ_{max}(MeOH)/nm 208 and 268; ν_{max}(film)/cm^{-1} 2391, 1766, 1682, 1448, 1265 and 740; δ_H($CDCl_3$) 1.52 (d, *J* 7.1, 3H, CH_3), 1.91 (m, 1H, C*H*CH_2N), 2.03 (m, 1H, C*H*CH_2N), 2.26 (m, 1H, C*H*CH_2CH_2N), 2.38 (m, 1H, C*H*CH_2CH_2N), 3.59 (m, 2H, CH_2N), 3.99 (dq, *J* 7.1, 2.4, 1H, C*H*CH_3), 4.20 (t, *J* 8.0, 1H, C*H*$CH_2CH_2CH_2N$), 4.93 [d, *J* 2.4, 1H, C(O)C*H*NH] and 7.26–7.62 (m, 5H, Ph); δ_C($CDCl_3$) 16.62, 23.41, 28.79, 37.67, 45.61, 58.09, 81.80, 128.37, 129.64, 135.18, 163.77 and 168.80; *m*/*z* (FAB) 339 (M^+ + 1).

(*S*)-*N*-(3-Hydroxy-2-phenylselenobutanoyl)prolinamide 10

Mp 119–122 °C; $[\alpha]_D$ −108.68 (*c* 0.85, $CHCl_3$); R_F 0.06 (silica, ethyl acetate); ν_{max}(film)/cm^{-1} 3360, 3200, 2972, 2877, 1678, 1628, 1431 and 740; δ_H($CDCl_3$) 1.39 (d, *J* 6.3, 3H, CH_3), 1.86–1.99 (m, 3H, C*HC*H_2CH_2N), 2.13 (m, 1H, C*H*CH_2CH_2N), 3.27 (dd, *J* 16.8, 7.5, 1H, CH*H*N), 3.63 (m, 1H, CH*H*N), 3.78 (d, *J* 8.2, 1H, *H*CSePh), 4.25 (dq, *J* 8.2, 6.3, 1H, C*H*CH_3), 4.38 (dd, *J* 7.7, 3.3, 1H, C*H*$CH_2CH_2CH_2N$), 6.14 (s, 1H, NH), 6.85 (s, 1H, NH) and 7.27–7.63 (m, 5H, Ph); δ_C($CDCl_3$) 21.73, 24.94, 28.71, 47.98, 50.28, 60.49, 69.91, 127.64, 129.27, 129.59, 136.41, 171.93 and 174.26; *m*/*z* (FAB) 357 (M^+ + 1) (Found: C, 50.43; H, 5.92; N, 7.54. Calc. for $C_{15}H_{20}N_2O_3Se$: C, 50.71; H, 5.67; N, 7.88%).

(*S*)-*N*-(3-Hydroxy-2-phenylselenobutanoyl)prolinamide 11

Mp 56–59 °C; $[\alpha]_D$ −69.29 (*c* 0.89, $CHCl_3$); R_F 0.07 (silica, ethyl acetate); ν_{max}(film)/cm^{-1} 3360, 3200, 2975, 2880, 1680, 1626, 1428 and 739; δ_H($CDCl_3$) 1.43 (d, *J* 6.3, 3H, CH_3), 1.87–1.99 (m, 3H, C*HC*H_2CH_2N), 2.34 (m, 1H, C*H*CH_2CH_2N), 3.41 (m, 2H, CH_2N), 3.59 (d, *J* 7.8, 1H, *H*CSePh), 3.87 (1H, br s, OH), 4.23 (m, 1H, C*H*CH_3), 4.59 (m, 1H, C*H*$CH_2CH_2CH_2N$), 5.70 (s, 1H, NH), 6.73 (s, 1H, NH) and 7.28–7.65 (m, 5H, Ph); δ_C($CDCl_3$) 21.14, 25.25, 27.74, 47.94, 49.28, 59.93, 69.07, 126.28, 129.42, 129.70, 136.54, 172.67 and 174.18; *m*/*z* (FAB) 357 (M^+ + 1) (Found: C, 50.37; H, 5.89; N, 7.56. Calc. for $C_{15}H_{20}N_2O_3Se$: C, 50.71; H, 5.67; N, 7.88%).

Acetylation of (*S*)-*N*-(3-hydroxy-2-phenylselenobutanoyl)-prolinamide 10 and 11

The reaction was carried out with acetic anhydride (1.1 equiv.) and pyridine (1.1 equiv.) in CH_2Cl_2 to give **12** and **13** as colourless oils.

(*S*)-*N*-(3-Acetoxy-2-phenylselenobutanoyl)prolinamide 12. $[\alpha]_D$ −144.55 (*c* 0.855, $CHCl_3$); R_F 0.13 (silica, ethyl acetate); ν_{max}(film)/cm^{-1} 3350, 3200, 2990, 1738, 1686, 1636, 1430 and 1237; δ_H($CDCl_3$) 1.49 (d, *J* 6.3, 3H, CHCH_3), 1.88 [3H, s, C(O)CH_3], 2.00–2.21 (m, 3H, C*HC*H_2CH_2N), 2.33 (m, 1H, C*H*CH_2CH_2N), 3.36–3.71 (m, 2H, CH_2N), 4.01 (d, *J* 9.0, 1H, *H*CSePh), 4.46 (dd, *J* 7.2, 1.8, 1H, C*H*$CH_2CH_2CH_2N$), 5.33 (dq, *J* 9.0, 6.3, 1H, C*H*CH_3), 5.91 (s, 1H, NH), 7.01 (s, 1H, NH) and 7.28–7.64 (m, 5H, Ph); δ_C($CDCl_3$) 18.55, 21.24, 25.14, 27.60, 47.86, 48.72, 60.06, 71.93, 126.30, 129.37, 136.29, 169.97 and 170.24; *m*/*z* (FAB) 399 (M^+ + 1).

(*S*)-*N*-(3-Acetoxy-2-phenylselenobutanoyl)prolinamide 13. $[\alpha]_D$ −13.12 (*c* 1.6, $CHCl_3$); R_F 0.15 (silica, ethyl acetate); ν_{max}(film)/cm^{-1} 3360, 3200, 2980, 1738, 1686, 1636, 1429, 1238 and 749; δ_H($CDCl_3$) 1.55 (d, *J* 6.3, 3H, CH_3), 1.91 [3H, s, C(O)CH_3], 2.00–2.18 (m, 3H, C*HC*H_2CH_2N), 2.32 (m, 1H, C*H*CH_2CH_2N), 3.51 (m, 2H, CH_2N), 3.92 (d, *J* 8.4, 1H, *H*CSePh), 4.61 (dd, *J* 8.1, 1.6, 1H, C*H*$CH_2CH_2CH_2N$), 5.33 (m, 1H, C*H*CH_3), 5.92 (s, 1H, NH), 7.05 (s, 1H, NH) and 7.28–7.65 (m, 5H, Ph); δ_C($CDCl_3$) 18.65, 21.38, 25.30, 27.76, 47.91, 50.26, 61.13, 71.30, 125.16, 129.77, 136.18, 138.83, 174.52 and 178.02.

(*S*)-*N*-(β-Methylcrotonyl)prolinamide 14. This compound was analogously prepared as described for **1**. Mp 151–153 °C; $[\alpha]_D$ −209.82 (*c* 0.79, $CHCl_3$); R_F 0.1 (silica, ethyl acetate); δ_H($CDCl_3$) 1.82 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.86–1.99 (m, 3H, C*HC*H_2CH_2N), 2.34 (m, 1H, C*H*CH_2CH_2N), 3.54 (m, 2H, CH_2N), 4.63 (dd, *J* 5.5, 2.5, 1H, C*H*$CH_2CH_2CH_2N$) and 5.85 [s, 1H, C*H*=$C(CH_3)_2$].

Cyclofunctionalization of (*S*)-*N*-(β-methylcrotonyl)prolinamide 14. To a solution of (*S*)-*N*-(β-methylcrotonoyl)prolinamide **14** (398 mg, 2.0 mmol) in acetonitrile (15 ml) were added silver trifluoromethanesulfonate (1.04 g, 4.0 mmol) in acetonitrile (12 ml), and then benzeneselenyl bromide (0.85 g, 3.6 mmol) and dimethylformamide (3.1 ml, 40 mmol) in acetonitrile (12 ml). The resulting mixture was stirred at ambient temperature for 12 h, after which it was treated with saturated aqueous $NaHCO_3$, and extracted with methylene dichloride. The extract was washed with brine, dried and evaporated to give the crude product, column chromatography of which afforded **15** (157.2 mg, 22.4%) as a yellow solid and **16** (364.8 mg, 49.4%) and **17** (98.6 mg, 13.3%) as colourless oils.

(9a*S*)-3,3-Dimethyl-4-phenylselenooctahydropyrrolo[1,2-*a*]-[1,4]diazepine-1,5-dione 15. Mp 190–191.5 °C; $[\alpha]_D$ −14.54 (*c* 1.00, $CHCl_3$); R_F 0.77 (silica, MeOH–CH_2Cl_2, 1:10); ν_{max}-(film)/cm^{-1} 1649, 1437 and 735; δ_H($CDCl_3$) 1.27 (s, 3H, CH_3),

Table 2 Crystal data for compounds **2**, **3**, **8** and **9**

Compound	**2**	**3**	**8**	**9**
Empirical formula	$C_{20}H_{20}N_2O_2Se$	$C_{20}H_{18}N_2O_2Se$	$C_{15}H_{18}N_2O_2Se$	$C_{15}H_{18}N_2O_2Se$
M	399.34	397.32	337.27	337.27
Crystal system	orthorhombic	monoclinic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a/Å	8.783(1)	12.681(1)	5.3445(4)	5.271(1)
b/Å	11.959(1)	5.523(2)	10.4678(8)	10.181(2)
c/Å	17.288(1)	12.846(7)	26.549(3)	27.974(6)
β/°		92.88(3)		
V/Å^3	1815.7(3)	898.6(6)	1485.3	1501.2(5)
Z	4	2	4	4
D_c/g cm^{-3}	1.460	1.469	1.508	1.492
μ/cm^{-1}	20.83	21.05	25.31	25.04
F(000)	816	404	688	688
Crystal size	0.35 × 0.30 × 0.10 mm	0.45 × 0.25 × 0.20 mm	0.40 × 0.20 × 0.15 mm	0.45 × 0.35 × 0.30 mm
θ range for data collection	2.07 to 23.97°	1.59 to 24.97°	1.53 to 22.95°	2.13 to 21.99°
Index ranges	$h = 0 \longrightarrow 10$	$h = -15 \longrightarrow 15$	$h = 0 \longrightarrow 5$	$h = 0 \longrightarrow 5$
	$k = 0 \longrightarrow 13$	$k = 0 \longrightarrow 6$	$k = 0 \longrightarrow 11$	$k = 0 \longrightarrow 10$
	$l = 0 \longrightarrow 19$	$l = 0 \longrightarrow 15$	$l = 0 \longrightarrow 29$	$l = 0 \longrightarrow 29$
Reflections collected	1639	1846	1236	1114
Independent reflections	1639	1762	1236	1114
Refinement method	Full-matrix least squares on F^2			
Data/parameters	1639/226	1762/226	1236/181	1114/173
Goodness-of-fit on F^2	1.040	1.034	1.098	1.097
Absolute structure parameter	0.02(3)	0.01(2)	−0.11(6)	0.00(5)
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.045$, $wR_2 = 0.093$	$R_1 = 0.044$, $wR_2 = 0.092$	$R_1 = 0.072$, $wR_2 = 0.167$	$R_1 = 0.069$, $wR_2 = 0.179$
R Indices (all data)	$R_1 = 0.063$, $wR_2 = 0.103$	$R_1 = 0.066$, w$R_2 = 0.103$	$R_1 = 0.100$, $wR_2 = 0.185$	$R_1 = 0.088$, $wR_2 = 0.196$
Largest diff. Peak and hole	0.276 and −0.357 e Å^{-3}	0.335 and −0.372 e Å^{-3}	0.536 and −0.716 e Å^{-3}	0.382 and −0.905 e Å^{-3}

R indicies; $R_1 = [\Sigma||F_o| - |F_c||]/\Sigma|F_o|$ (based on F), $wR_2 = \{[\Sigma w(|F_o^2 - F_c^2|)^2]/[\Sigma w(F_o^2)^2]\}^{\frac{1}{2}}$ (based on F^2).

1.34 (s, 3H, CH_3), 1.78 (m, 2H, CH_2CH$_2$N), 2.11 (m, 1H, CHCH$_2$CH$_2$N), 2.55 m, 1H, CHCH$_2$CH$_2$N), 3.53 (m, 2H, CH_2N), 4.42 (dd, J 7.8, 4.9, 1H, CHCH$_2$CH$_2$CH$_2$N), 4.46 [s, 1H, C(O)CHSePh] and 7.19–7.59 (m, 5H, Ph); δ_C($CDCl_3$) 22.84, 26.82, 28.97, 31.65, 47.09, 58.27, 58.72, 59.94, 127.76, 129.17, 130.48, 134.20, 167.41 and 169.51; m/z (EI) [Found (HRMS, EI): m/z 352.0691. Calc. for $C_{16}H_{20}N_2O_2Se$: 352.0690].

(*S*)-*N*-(3-Hydroxy-3-ethyl-2-phenylselenobutanoyl)prolinamide 16. [α]$_D$ −107.04 (c 2.7, MeOH); R_F 0.08 (silica, ethyl acetate); δ_H($CDCl_3$) 1.37 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.60–2.19 (m, 4H, CH_2CH_2CH$_2$N), 2.79 (m, 1H, CHHN), 3.34 (m, 1H, CHHN), 3.93 (s, 1H, HCSePh), 4.40 (dd, J 7.8, 3.0, 1H, CHCH$_2$CH$_2$CH$_2$N), 4.95 (s, 1H, OH), 5.71 (s, 1H, NH), 6.94 (s, 1H, NH) and 7.28–7.72 (m, 5H, Ph); δ_C($CDCl_3$) 24.88, 28.55, 29.02, 48.21, 54.52, 55.43, 60.06, 72.55, 128.14, 129.27, 129.60, 136.72, 173.35 and 174.04; m/z (FAB) 371 ($M^+ + 1$).

(*S*)-*N*-(3-Hydroxy-3-methyl-2-phenylselenobutanoyl)prolinamide 17

[α]$_D$ +35.12 (c 0.885, CH_3OH); R_F 0.11 (silica, ethyl acetate); δ_H($CDCl_3$) 1.37 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.66–1.95 (m, 3H, CHCH$_2$CH$_2$N + CH_2CH$_2$N), 2.39 (m, 1H, CHCH$_2$-CH$_2$N), 2.76 (m, 1H, CHHN), 3.14 (dd, J 17.0, 8.6, 1H, CHHN), 3.75 (s, 1H, HCSePh), 4.67 (ad, J 6.1, 1H, CHCH$_2$-CH$_2$CH$_2$N), 4.90 (s, 1H, OH), 5.61 (s, 1H, NH), 6.87 (s, 1H, NH) and 7.28–7.72 (m, 5H, Ph); δ_C($CDCl_3$) 25.15, 27.66, 28.72, 28.90, 48.9, 55.46, 59.54, 72.16, 126.30, 129.24, 129.77, 136.48, 172.97 and 174.79; m/z (FAB) 371 ($M^+ + 1$).

(9a*S*)-3,3-Dimethyloctahydropyrrolo[1,2-*a*][1,4]diazepine-1,5-dione 18. To a solution of **15** (75.2 mg, 0.21 mmol) in THF (3 ml) was added a solution of nickel(II) chloride hexahydrate (101.8 mg, 0.42 mmol) in MeOH (3 ml) at ambient temperature. The mixture was cooled in an ice-bath and treated with sodium borohydride (48.6 mg, 1.28 mmol), added in small portions. After an additional 10 min at 0 °C, the mixture was filtered through Celite and chromatographed to give product **18** (42.0 mg, quantitative yield) as a white solid, mp 195–197 °C; [α]$_D$ −120.33 (c 1.26, $CHCl_3$); R_F 0.44 (silica, MeOH–CH_2Cl_2, 1:10); ν_{max}(film)/cm^{-1} 1655, 1444, 1262 and 854; δ_H($CDCl_3$) 1.34 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.83 (m, 2H, CH_2CH$_2$N), 2.16 (m, 1H, CHCH$_2$CH$_2$N), 2.47 [dd, J 14.1, 1.8, 1H, C(O)CHH], 2.67 (m, 1H, CHCH$_2$CH$_2$N), 3.07 [d, J 14.1, 1H, C(O)CHH), 3.56 (m, 2H, CH_2N), 4.42 (dd, J 8.1, 4.8, 1H, CHCH$_2$CH$_2$CH$_2$N) and 5.83 (s, 1H, NH); δ_C($CDCl_3$) 23.30, 28.83, 29.77, 32.94, 46.45, 49.94, 53.34, 59.64, 168.61 and 169.40.

X-Ray crystal structure determinations of compounds 2, 3, 8 and 9

A crystal of each of the compounds **2**, **3**, **8** and **9** was sealed in a Lindemann glass capillary tube and mounted on an Enraf-Nonius CAD4 diffractometer equipped with graphite-monochromated Mo-Kα ($\lambda = 0.710\,69$ Å) radiation. Cell parameters and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections at 293 K. The intensities of 3 standard reflections, recorded every 3 h of X-ray exposure, showed no systematic changes. The crystal data for compounds **2**, **3**, **8** and **9** are summarized in Table 2. The intensity data were corrected for Lorentz and polarization effects. Empirical absorption corrections were also applied (XABS2).[14] Their structures were solved by direct methods (SHELXS-86).[15] For **9**, the phenylselenyl group was disordered over two sites and the sum of their occupancies was fixed to 1 (0.493 + 0.507). Full-matrix least-squares refinement[16] was employed with anisotropic thermal parameters for all non-hydrogen atoms. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/176.

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References

1 (*a*) K. E. Harding and T. H. Tiner, in *Comprehensive Organic Synthesis*, ed. M. F. Semmelhack, Pergamon Press, Oxford, 1991, vol. 4, p. 363; (*b*) J. Mulzer, in *Comprehensive Organic Synthesis*, ed. E. Winterfeldt, Pergamon Press, Oxford, 1991, vol. 6, p. 324; (*c*) J. E. G. Kemp, in *Comprehensive Organic Synthesis*, ed. S. V. Ley, Pergamon Press, Oxford, 1991, vol. 7, p. 469; (*d*) K. A. Swiss and D. C. Liotta, in *Comprehensive Organic Synthesis*, ed. S. V. Ley, Pergamon Press, Oxford, 1991, vol. 7, p. 515.
2 J. E. Baldwin, *J. Chem. Soc.*, *Chem. Commun.*, 1976, 734.
3 (*a*) K. C. Nicolaou, N. A. Petasis and D. A. Claremon, in *Organic Selenium Chemistry*, ed. D. Liotta, John Wiley & Sons, New York, 1987; (*b*) C. Paulmier, *Selenium Reagents and Intermediates in Organic Chemistry*, Pergamon Press, Oxford, 1986; (*c*) D. L. J. Clive, C. K. Wong, W. A. Kiel and S. M. Menchen, *J. Chem. Soc.*, *Chem. Commun.*, 1978, 379; (*d*) R. Grigg, M. Hadjisoteriou, P. Kennewell, J. Markandu and M. Thornton-Pett, *J. Chem. Soc.*, *Chem. Commun.*, 1993, 1340; (*e*) N. De Kimpe and M. Boelens, *J. Chem. Soc.*, *Chem. Commun.*, 1993, 916; (*f*) M. Tiecco, L. Testaferri, M. Tingolo and L. Bangoli, *J. Chem. Soc.*, *Chem. Commun.*, 1995, 235.
4 (*a*) E. J. Corey, M. Shibasaki and J. Knolle, *Tetrahedron Lett.*, 1977, 1625; (*b*) Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi and M. Minobe, *J. Am. Chem. Soc.*, 1984, **106**, 1079; (*c*) A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1986, **51**, 1724.
5 (*a*) A. J. Biloski, R. D. Wood and B. Ganem, *J. Am. Chem. Soc.*, 1982, **104**, 3233; (*b*) A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1987, **52**, 2018; (*c*) H. Takahata, T. Takmatsu and T. Yamazaki, *J. Org. Chem.*, 1989, **54**, 4812.
6 (*a*) S. Knapp and A. T. Levorse, *J. Org. Chem.*, 1988, **53**, 4006; (*b*) T. W. Balko, R. S. Brinkmeyer and N. H. Terando, *Tetrahedron Lett.*, 1989, 2045; (*c*) G. Rajendra and M. J. Miller, *J. Org. Chem.*, 1987, **52**, 4471.
7 A preliminary account of this work was published. S. K. Chung, T. H. Jeong and D. H. Kang, *Tetrahedron: Asymmetry*, 1997, **8**, 5.
8 S. Murata and T. Suzuki, *Chemistry Lett.*, 1987, 849.
9 T. J. Back, *J. Chem. Soc.*, *Chem. Commun.*, 1984, 1417.
10 A. Toshimitsu, H. Owada, S. Uemura and M. Okano, *J. Chem. Soc.*, *Chem. Commun.*, 1981, 546.
11 (*a*) B. W. Bycroft and G. R. Lee, *J. Chem. Soc.*, *Chem. Commun.*, 1975, 988; (*b*) N. Izumiya, S. Lee, T. Kanmera and H. Aoyagi, *J. Am. Chem. Soc.*, 1977, **99**, 8346; (*c*) T. Kanmera, S. Lee, H. Aoyagi and N. Izumiya, *Tetrahedron Lett.*, 1979, 4483.
12 S. K. Chung and K. H. Paik, unpublished results.
13 (*a*) O. W. Griffith, *Ann. Rev. Biochem.*, 1986, **55**, 855; (*b*) D. C. Cole, *Tetrahedron*, 1994, **50**, 9517; (*c*) E. Juaristi, D. Quintana and J. Esclante, *Aldrichimica Acta*, 1994, **27**, 3.
14 S. Parkin, B. Moezzi and H. Hope, *J. Appl. Cryst.*, 1995, **28**, 53.
15 G. M. Sheldrick, SHELXS-86, *Acta Crystallogr.*, *Sect. A*, 1990, **46**, 467.
16 G. M. Sheldrick, SHELXL-93. University of Göttingen, Germany, 1993.

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