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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2758–2767

Selenium promoted synthesis of enantiopure pyrrolidines starting from chiral aminoalcohols

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Received 30 August 2007; accepted 5 November 2007
Available online 28 November 2007

Abstract—Starting from commercially available enantiomerically pure aminoalcohols and using simple conversions promoted by organoselenium reagents, several enantiomerically pure substituted pyrrolidines were prepared. After double protections (*R*)- or (*S*)-2-phenylglycinols were converted into the β-amino selenides by displacing the tosyl group with phenyl selenolate anions. The phenylseleno group was then substituted by an allyl group by treatment with allyltributyltin and AIBN. The reaction of these allylic derivatives with electrophilic phenylselenium reagents afforded selenium containing pyrrolidines as the result of a 5-*exo*-*trig* cyclization. The pyrrolidine derivatives thus obtained were reductively deselenylated with triphenyltin hydride and AIBN. Moreover, the selenides were converted into the selenones, which easily gave substitution with different nucleophiles. Enantiopure 2,5-pyrrolidines containing azido, methylthio, cyano and iodo groups were thus obtained.

1. Introduction

Pyrrolidine ring systems are present in a large number of biologically active natural products as well as in numerous therapeutic agents.[1] They often also serve as pivotal key intermediates in the synthesis of pyrrolizidine and indolizidine alkaloids.[2] Furthermore, some pyrrolidine derivatives have found employment as organocatalysts,[3] as chiral ligands for asymmetric catalysis and as chiral auxiliaries.[4] Although many racemic syntheses of this ring system have been reported, few general methods are available for their preparation in enantiomerically pure forms.[5] A very convenient procedure can involve cyclofunctionalization reactions promoted by selenium reagents.[6] In these cases olefinic primary amines do not cyclize readily while N-protected olefinic primary amines do.[7] Of particular importance is the possibility of performing either reagent-controlled or substrate-controlled asymmetric cyclization reactions from which enantiomerically enriched or enantiopure heterocycles can be obtained.[8] Despite the numerous reagent-controlled asymmetric cyclization reactions leading to oxygen-containing heterocycles reported in the literature, only sporadic examples[9,10] of the application of these cyclizations to the synthesis of nitrogen-containing heterocycles have been described. Our research group has reported the syntheses of different nitrogen-containing heterocycles with high diastereoselectivity through reagent-controlled asymmetric selenocyclization of alkenes.[11] At the same time we have carried out the synthesis of enantiomerically pure oxygen-containing heterocycles starting from commercially available enantiopure compounds and using simple conversions promoted by electrophilic phenylselenium reagents.[12] Herein we report a simple procedure to effect the substrate-controlled asymmetric cyclizations of easily available N-protected alkenyl amines from which valuable disubstituted pyrrolidine derivatives can be obtained in enantiomerically pure form.

2. Results and discussion

The starting compound necessary for the present investigation was the commercially available aminoalcohol, (*R*)-(−)-2-phenylglycinol **1** (ee 99%) (Scheme 1), which was transformed into the *N*-Boc derivative **2** by treatment with stoichiometric amounts of di-*tert*-butyl dicarbonate and triethylamine.[12d] The *N*-Boc protected aminoalcohol **2**

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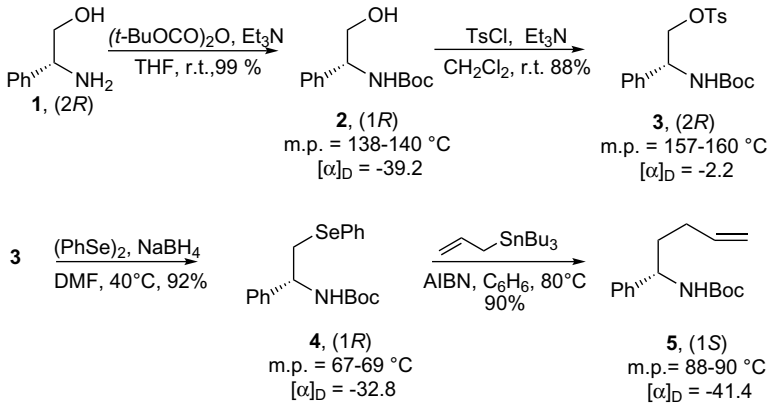
doi:10.1016/j.tetasy.2007.11.003



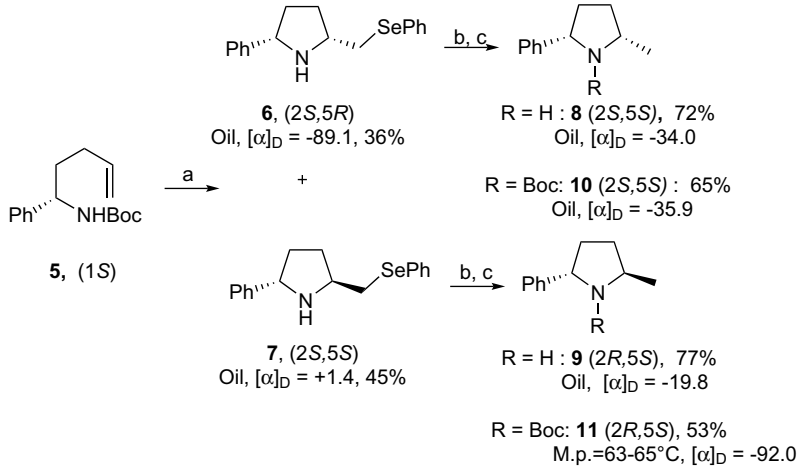
Scheme 1.

was easily converted into the corresponding *O*-tosyl derivative **3**.[13] This product was sufficiently pure to be used for the next step without purification by column chromatography. Upon treatment with phenyl selenolate anion, produced in situ by diphenyl diselenide and sodium borohydride, compound **3** gave the β-amino selenide **4**. Finally the phenylseleno group was replaced by an allyl group by treatment with allyltributyltin and AIBN in refluxing benzene to give *tert*-butyl [(1*S*)-1-phenylpent-4-en-1-yl]carbamate **5** (Scheme 1).

The key step of the present reaction sequence is the 5-*exo-trig* selenocyclization reaction of this N-protected alkenyl amine promoted by *N*-(phenylseleno)phthalimide in the presence of $BF_3{\cdot}Et_2O$ as a catalyst. NMR analysis of the crude reaction mixture indicated that two diastereomeric *N*-Boc pyrrolidines were obtained. These, however, could not be separated by column chromatography. Thus, when TLC analysis of the reaction mixture indicated that the starting product **5** was completely consumed, an excess of $BF_3{\cdot}Et_2O$ was added to effect the *N*-Boc bond cleavage. Proton NMR analysis of the reaction mixture indicated that the two 2-phenyl-5-[(phenylselenomethyl)]pyrrolidines **6** and **7** were formed in a 1:1.2 ratio. The mixture was chromatographed and the two products were obtained in an enantiomerically pure form (Scheme 2). The structures of these two diastereoisomers were determined by NMR spectroscopy on the basis of the results of NOESY experiments. In compound **6** a strong dipolar interaction was observed between the protons at the 2- and 5-positions, whereas in compound **7**, a strong dipolar interaction was observed between the proton at the 2-position and the two protons of the CH_2SePh group at the 5-position.

Pyrrolidines **6** and **7** were then treated separately with triphenyltin hydride and AIBN in refluxing benzene to afford (2*S*,5*S*)-2-methyl-5-phenylpyrrolidine **8**[5c] and (2*R*,5*S*)-2-methyl-5-phenylpyrrolidine **9** (Scheme 2). The enantiomeric purity of pyrrolidines **8** and **9** was confirmed by HPLC analysis, on the chiral columns (*R*,*R*) Whelk-O 1 and Chiracel OD-H, respectively, of their *N*-Boc derivates **10** and **11**, which were easily prepared in *one pot* by deselenylation and *N*-Boc protection of **6** and **7** (Scheme 2).

A similar synthetic sequence was also effected starting from (*S*)-(+)-2-phenyl glycinol *ent*-**1** (ee 99%). Following the procedures described above for **1**, compounds *ent*-**2**, *ent*-**3**, *ent*-**4** and *ent*-**5** were prepared. The selenium promoted



Scheme 2. Reagents and conditions: (a) *N*-PSP, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; (b) Ph_3SnH, AIBN, C_6H_6, 80 °C; (c) $(t\text{-BuOCO})_2$, Et_3N, THF, rt.

cyclization afforded the two 2-phenyl-5-[(phenylselenomethyl)]pyrrolidines *ent*-**6** and *ent*-**7** in a 1:1.2 ratio. The deselenenylated pyrrolidines *ent*-**8** and *ent*-**9** and their *N*-Boc derivatives *ent*-**10** and *ent*-**11** were prepared as described above for the enantiomeric compounds (Scheme 3).

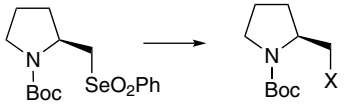
The presence of the organoselenium functionality in the cyclization products **6** and **7** allows the introduction of several other groups to be easily effected. The radical substitution of the phenylseleno moiety by an allyl group, for instance, gives products, which can be used to effect other cyclization reactions thus affording interesting bicyclic compounds.[12b] Other interesting processes are the deselenenylation reactions, which occur by substitution after conversion of the PhSe group into a good leaving group such as the selenone which is obtained by simple oxidation.[8b,14] The leaving ability of the selenonyl group has already been observed, in intermolecular[15] as well as in intramolecular substitution reactions,[16] using carbon, oxygen or nitrogen[17] nucleophiles. The intramolecular process gives rise to various types of heterocyclic compounds.

To find the best reaction conditions to effect similar substitution reactions in the enantiopure pyrrolidines described above, we employed the easily available *tert*-butyl (2*S*)-2-[(phenylselenonyl)methyl]pyrrolidine-1-carboxylate **14** as a model substrate (Scheme 4). This compound was easily synthesized starting from the tosyl derivate **12**, which in turn was easily obtained[18] by the commercially available *N*-Boc-L-prolinol (ee 98%). The substitution of the tosyl group by the phenyl selenolate anion afforded selenide **13**, which was oxidized to selenone **14** using Oxone®, under very mild reaction conditions.[19] The reaction mixture was poured into water and extracted with dichloromethane. The solvent was evaporated and the crude selenone **14** (70% yield) was sufficiently pure (TLC) enough to be used without further purification, as previously reported in several cases.[8b,15c,17]

Attempts to purify the crude selenone by column chromatography or by crystallization induced decomposition of the product. The formation of the selenone, however, was clearly demonstrated by TLC analysis (R_f lower than that of the selenide and higher than that of the selenoxide). Further indications came from a rapid and careful NMR analysis of the crude product. The ^{77}Se NMR signals of *N*-Boc selenide **13** appeared at 253.4 and 264.6 ppm, while in the *N*-Boc selenone **14** were deshielded at 984.9 and 986.9 ppm.[14b] These two absorptions suggest that, at room temperature, owing to the presence of the *N*-Boc substituent, the molecule is present as two distinct conformers.

Several preliminary experiments were carried out to find the best experimental conditions to effect the substitution of the selenonyl group of **14** with different nucleophiles. We finally found that, under the experimental conditions described in Table 1, the azido, cyano, methylthio and iodo groups could be introduced to afford valuable pyrrolidine derivatives in good yield and in an enantiomerically pure form (Table 1).

Table 1.

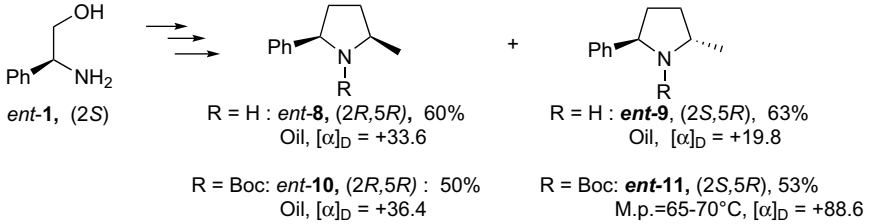


14(2*S*) **15a-d**

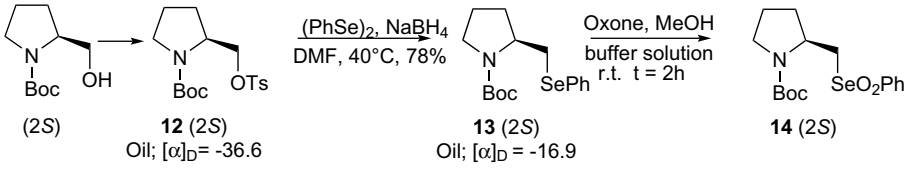
Reagent[a]	Reaction conditions	X	Yield (%)	$[\alpha]_D$
NaN_3[b]	DMF, 80 °C, 2 h	N_3	**15a**: 70	−47.4
KCN[c]	DMF, 40 °C, 1 h	CN	**15b**: 73	−87.7
$NaSCH_3$[b]	DMF, 80 °C, 1 h	SMe	**15c**: 86	−51.7
NaI	Acetone, 20 °C, 5 h	I	**15d**: 64	−35.2

[a] Two equivalents of the reagent was employed.
[b] Two equivalents of 15-Crown-5 was also employed.
[c] Two equivalents of 18-Crown-6 was also employed.

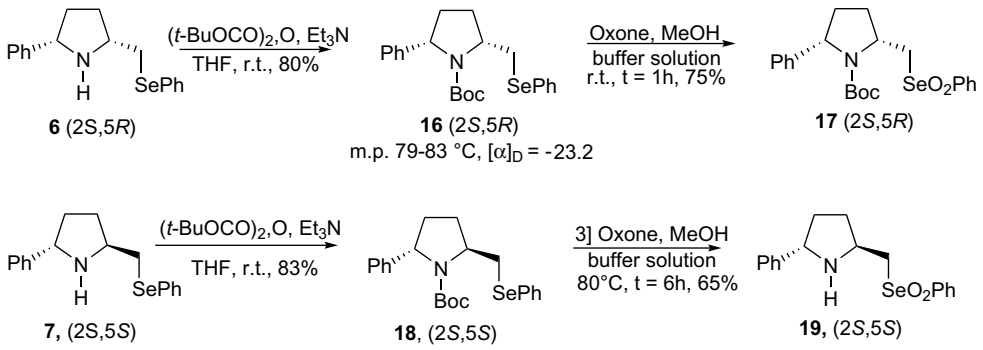
After these encouraging results we then applied similar reaction conditions to the substitution reactions of pyrrolidines **6** and **7**. These were converted into their *N*-Boc derivatives **16** and **18** and then oxidized to the selenones



Scheme 3.



Scheme 4.



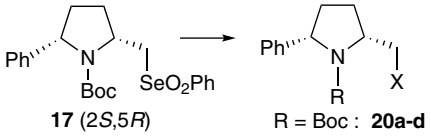
Scheme 5.

(Scheme 5). From the *cis* pyrrolidine **6** selenone **17** was easily obtained under the usual conditions[19] whereas the preparation of the selenone deriving from the *trans* pyrrolidine **7** required higher temperatures and 3 M equiv of Oxone®. Under these conditions the reaction product was the unprotected selenone **19**. The crude selenone intermediates **17** (75% yield) and **19** (65% yield) were directly used without further purification.

The results obtained from the substitution reactions carried out on the *cis*-2,5-disubstituted selenone **17**, under the reaction conditions indicated, are reported in Table 2. The enantiomerically pure azido, cyano, methylthio and iodo pyrrolidines **20a–d** were obtained in satisfactory to good yields. Compound **20c** was accompanied by the corresponding unprotected pyrrolidine derivate **20c′**.

A different situation was encountered in the case of the isomeric *trans* selenone. First of all, attempts to transform selenone **19** into the corresponding *N*-Boc protected derivative gave complex reaction mixtures. The substitution reactions were therefore carried out on compound **19**. In this case, however, to effect the displacement of the selenonyl group by the azido and cyano groups, much higher reaction temperatures and longer reaction times were required (Table 3). As indicated in Table 3, under these conditions, the desired substitution products were accompanied by considerable amounts of the elimination

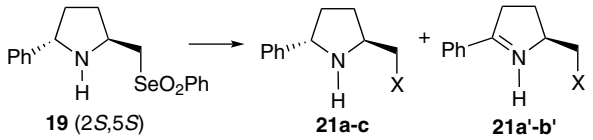
Table 2.



Reagent[a]	Reaction conditions	X	Yield (%)	$[\alpha]_D$
NaN_3	DMF, 80 °C, 1 h	N_3	**20a**: 92	−37.2
KCN[b]	DMF, 80 °C, 3 h	CN	**20b**: 45	+12.5
$NaSCH_3$[c]	DMF, 80 °C, 1 h	SMe	**20c**: 50	−19.6
			20c′: 15	−69.9
NaI	DMF, 80 °C, 3 h	I	**20d**: 47	−25.2

[a] Five equivalents of the reagent was employed in the first three cases, and 2 equiv in the case of NaI.
[b] Two equivalents of 18-Crown-6 was also employed.
[c] Two equivalents of 15-Crown-5 was also employed.

Table 3.



Reagent[a]	Reaction conditions	X	Yield (%)	$[\alpha]_D$
NaN_3	DMF, 160 °C, 8 h	N_3	**21a**: 40	−30.9
			21a′: 22	+38.4
KCN[b]	DMF, 160 °C, 6 h	CN	**21b**: 32	−20.3
			21b′: 26	
$NaSCH_3$[c]	DMF, 80 °C, 1 h	SMe	**21c**: 63	+26.6

[a] Five equivalents of the reagent was employed in the first three cases, and 2 equiv in the case of NaI.
[b] Two equivalents of 18-Crown-6 was also employed.
[c] Two equivalents of 15-Crown-5 was also employed.

products **21a′** and **21b′**. The reaction with the strongly nucleophilic methanethiolate occurred easily, whereas different attempts to effect the substitution with sodium iodide did not give acceptable results. Thus, starting from the selenones some interesting enantiomerically pure 2,5-*cis* and *trans*-disubstituted pyrrolidines could be obtained. Derivatives **20a–d** and **21a–c** are useful compounds, which are susceptible to further manipulations.

3. Conclusions

Starting from commercially available enantiopure aminoalcohols and using simple conversions promoted by organoselenium reagents, several enantiomerically pure *cis* and *trans*-2,5-disubstituted pyrrolidines were synthesized. The key step of these syntheses is the substrate-controlled asymmetric cyclization of the *N*-Boc protected δ-alkenyl amines promoted by *N*-(phenylseleno)phthalimide. Moreover, the selenides thus obtained were converted into the selenones, which could be substituted by different nucleophiles to afford interesting enantiopure 2,5-pyrrolidines containing azido, methylthio, cyano and iodo substituents.

4. Experimental

All new compounds were characterized by MS, ^1H and ^{13}C and in some cases ^{77}Se NMR spectra. GC analyses and MS

spectra were carried out with an HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass Selective Detector; for the ions containing selenium only the peaks arising from the selenium-80 isotope are given. ^{1}H, ^{77}Se and ^{13}C NMR spectra were recorded at 400, 76.27 and 100.62 MHz, respectively, on a Bruker DRX 400 instrument; $CDCl_3$ was used as solvent and TMS as standard. The NMR spectra were recorded at room temperature. At this temperature in most of the *N*-Boc compounds two conformers are present, which give distinct or broad signals. In some of these cases the NMR spectra were therefore recorded at higher temperatures (315 K or 325 K) so that the merging of the signals could be observed. HPLC analyses were performed on an HP 1100 instrument equipped with a chiral column and a UV detector. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

4.1. Starting products

Commercial (*R*)-(+)-2-phenylglycinol (ee 99%), (*S*)-(+)-2-phenylglycinol (ee 99%) and *N*-Boc-L-prolinol (ee 98%) were used without further purification. The (2*R**)-phenylglycinol, necessary as a reference for the HPLC analyses, was prepared according to the procedure described in the literature.[20]

4.2. Protection of aminoalcohols 1 and *ent*-1 and of pyrrolidines 6 and 7

The *N*-Boc protected (*R*)- and (*S*)-phenylglycinols **2** and *ent*-**2** were synthesized from the corresponding aminoalcohols **1** and *ent*-**1** by treatment with stoichiometric amounts of triethylamine and di-*tert*-butyl dicarbonate in tetrahydrofuran at room temperature according to the standard procedure[12d] (Scheme 1). The same method was applied for the *N*-Boc protections of pyrrolidines **6** and **7** to prepare pyrrolidines **16** and **18**. These were isolated in their pure form by crystallization from light petroleum. (Scheme 5). The protection of **8** and **9** was effected in *one pot* after deselenenylation and is described below (Scheme 2).

The *N*-Boc protected aminoalcohols **2** and *ent*-**2** were then converted into the corresponding tosyl derivatives **3** and *ent*-**3** by treatment with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane[13] (Scheme 1).

The physical and spectral data of compounds **2** and *ent*-**2** are reported in the literature[12d] while those of compounds **3**, *ent*-**3**, **16** and **18** are reported below.

4.2.1. (2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl-4-methylbenzenesulfonate, 3. Mp = 157–160 °C; $[\alpha]_D^{23} = -2.2$ (*c* 2.03, $CHCl_3$). ^{1}H NMR: δ 7.67 (d, 2H, $J = 8.3$ Hz), 7.32–7.15 (m, 7H), 5.15 (br s, 1H), 4.98–4.83 (m, 1H), 4.26 (dd, 1H, $J = 4.5$, 10.0 Hz), 4.17 (dd, 1H, $J = 5.8$, 10.0 Hz), 2.42 (s, 3H), 1.40 (s, 9H); ^{13}C NMR: δ 154.8, 144.9, 137.7, 132.3, 128.9 (two carbons), 128.7 (two carbons), 127.9, 127.8 (two carbons), 126.5 (two carbons), 80.1, 71.5, 53.5, 28.2 (three carbons), 21.6. Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.47; H, 6.35; N, 3.71.

4.2.2. (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl-4-methylbenzenesulfonate, *ent*-3. Mp = 156–160 °C; $[\alpha]_D^{32} = +2.1$ (*c* 2.11, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.38; H, 6.52; N, 3.69.

4.2.3. *tert*-Butyl (2*S*,5*R*)-2-phenyl-5-[(phenylseleno)methyl]pyrrolidine-1-carboxylate, 16. Mp = 79–83 °C; $[\alpha]_D^{22} = -23.2$ (*c* 2.14, $CHCl_3$); ^{1}H NMR (325 K): δ 7.58–7.55 (m, 2H), 7.33–7.19 (m, 8H), 4.87–4.84 (m, 1H), 4.29–4.23 (m, 1H), 3.68 (dd, 1H, $J = 3.0$, 11.8 Hz), 2.98 (dd, 1H, $J = 10.7$, 11.8 Hz), 2.32–2.22 (m, 1H), 2.17–2.06 (m, 1H), 1.96–1.87 (m, 2H), 1.29 (s, 9H); ^{13}C NMR (325 K): δ 154.7, 144.3, 132.5, 130.4, 129.0 (two carbons), 128.2 (two carbons), 126.7, 126.5 (two carbons), 125.5 (two carbons), 79.6, 63.2, 59.4, 33.9, 32.1, 29.8, 28.3 (three carbons); MS *m*/*z* (rel int.): 417 (9), 190 (61), 146 (100), 57 (33). Anal. Calcd for $C_{22}H_{27}NO_2Se$: C, 63.45; H, 6.54; N, 3.36. Found: C, 63.54; H, 6.46; N, 3.21.

4.2.4. *tert*-Butyl (2*S*,5*S*)-2-phenyl-5-[(phenylseleno)methyl]pyrrolidine-1-carboxylate, 18. Mp = 75–78 °C; $[\alpha]_D^{20} = -78.8$ (*c* 2.46, $CHCl_3$); *Major conformer*: ^{1}H NMR: δ 7.64–7.60 (m, 2H), 7.31–7.21 (m, 6H), 7.10–7.05 (m, 2H), 4.88–4.85 (m, 1H), 4.47–4.42 (m, 1H), 3.62 (dd, 1H, $J = 2.9$, 12.2 Hz), 2.95 (dd, 1H, $J = 9.9$, 12.2 Hz) 2.50–2.32 (m, 1H), 2.18–1.89 (m, 2H), 1.74–1.67 (m, 1H), 1.13 (s, 9H); ^{13}C NMR: δ 153.8, 144.1, 130.5, 129.0 (two carbons), 128.1 (two carbons), 126.6, 126.4 (two carbons), 125.6, 125.2 (two carbons), 79.4, 62.4, 58.6, 32.6, 31.0, 28.2 (three carbons), 27.4. *Minor conformer* (*distinct signals*): ^{1}H NMR: δ 5.05–5.02 (m, 1H), 4.26–4.22 (m,1H), 3.47 (dd, 1H, $J = 1.9$, 12.0 Hz), 2.79 (dd, 1H, $J = 10.8$, 12.0 Hz), 1.38 (s, 9H); ^{13}C NMR: δ 63.3, 59.5, 33.9, 29.9; MS *m*/*z* (rel int.): 417 (9), 246 (34), 190 (63), 146 (100), 91(13) 57(31). Anal. Calcd for $C_{22}H_{27}NO_2Se$: C, 63.45; H, 6.54; N, 3.36. Found: C, 63.58; H, 6.67; N, 3.47.

4.3. Synthesis of the β-amino selenides 4, *ent*-4 and 13

To a solution of diphenyl diselenide (4.2 mmol) in dimethylformamide sodium borohydride (8.3 mmol) was added at 40 °C. After 30 min, compounds **3**, *ent*-**3** or **12** (6.4 mmol) were added and the reactions were stirred overnight. The reaction mixture was poured into water and extracted with diethyl ether. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and evaporated under vacuum. Reaction products **4**, *ent*-**4** and **13** were obtained in a pure form after column chromatography of the residue on silica gel with a mixture of diethyl ether and light petroleum (from 5:95 to 10:90) as eluant. The products obtained and the reaction yields are reported in Schemes 1 and 4. Physical and spectral data are reported below.

4.3.1. *tert*-Butyl [(1*R*)-1-phenyl-2-(phenylseleno)ethyl]carbamate, 4. Mp = 67–69 °C; $[\alpha]_D^{22} = -32.8$ (*c* 2.14, $CHCl_3$). ^{1}H NMR: δ 7.52–7.49 (m, 2H), 7.33–7.15 (m, 8H), 5.18 (d, 1H, $J = 7.5$ Hz), 4.97–4.81 (m, 1H), 3.29–3.23 (m, 2H), 1.40 (s, 9H); ^{13}C NMR: δ 155.0, 133.0, 129.8 (two car-

bons), 129.1 (two carbons), 128.6 (two carbons), 127.6 (two carbons), 127.2, 126.3 (two carbons), 79.7, 54.5, 35.2, 28.3 (three carbons). Anal. Calcd for $C_{19}H_{23}NO_2Se$: C, 60.64; H, 6.16; N, 3.72. Found: C, 60.79; H, 6.25; N, 3.69.

4.3.2. *tert*-Butyl [(1*S*)-1-phenyl-2-(phenylseleno)ethyl]carbamate, *ent*-4. Mp = 67–68 °C; $[\alpha]_D^{18} = +32.9$ (*c* 2.24, $CHCl_3$). Anal. Calcd per $C_{19}H_{23}NO_2Se$: C, 60.64; H, 6.16; N, 3.72. Found: C, 60.75; H, 6.28; N, 3.85.

4.3.3. *tert*-Butyl (2*S*)-2-[(phenylseleno)methyl]pyrrolidine-1-carboxylate, 13. Oil; $[\alpha]_D^{23} = -16.9$ (*c* 2.14, $CHCl_3$); ^1H NMR (325 K): δ 7.56–7.55 (m, 2H), 7.26–7.19 (m, 3H), 4.08–3.99 (m, 1H), 3.50–3.27 (m, 3H), 2.96–2.82 (m, 1H), 2.09–1.98 (m, 1H), 1.96–1.72 (m, 3H), 1.44 (s, 9H); ^{13}C NMR (325 K): δ 154.2, 132.6, 130.4, 128.9 (two carbons), 126.7 (two carbons), 79.2, 57.3, 46.9, 31.9, 30.8, 28.5 (three carbons), 23.2; ^{77}Se NMR (room temperature): δ 253.4 and 264.6; MS *m*/*z* (rel int.): 341 (36), 268 (16), 170 (59), 157 (5), 114 (100), 91 (22), 70 (78), 57 (64). Anal. Calcd for $C_{16}H_{23}NO_2$ Se: C,56.47; H, 6.81; N, 4.12. Found: C, 56.49; H, 6.93; N, 4.24.

4.4. Synthesis of compounds 5 and *ent*-5 by radical allylation

To a solution of compounds **4** or *ent*-**4** (1 mmol) and a catalytic amount of AIBN in refluxing dry benzene (8 mL) allyltributyltin (5 mmol) was added in 4 h with a syringe pump under nitrogen. The progress of the reactions was monitored by TLC. The solvent was then carefully evaporated under vacuum. The allylated compounds **5** and *ent*-**5** were isolated in a pure form after column chromatography on silica gel using a mixture of diethyl ether and light petroleum (from 2:98 to 10:90) as eluant. Physical and spectral data are reported below.

4.4.1. *tert*-Butyl [(1*S*)-1-phenylpent-4-en-1-yl]carbamate, 5. Mp = 88–90 °C; $[\alpha]_D^{22} = -41.4$ (*c* 1.99, $CHCl_3$). ^1H NMR: δ 7.41–7.22 (m, 5H), 5.83 (ddt, 1H, $J = 6.2$, 10.1, 16.5 Hz), 5.07–4.96 (m, 2H), 4.89 (br s, 1H), 4.75– 4.52 (m, 1H), 2.10–2.00 (m, 2H), 1.95–1.78 (m, 2H), 1.42 (s, 9H); ^{13}C NMR: δ 155.1, 142.7, 137.6, 128.5 (two carbons), 127.1, 126.3 (two carbons), 115.2, 79.3, 54.4, 36.0, 30.3, 28.3 (three carbons). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.55; H, 8.94; N, 5.43.

4.4.2. *tert*-Butyl [(1*R*)-1-phenylpent-4-en-1-yl]carbamate, *ent*-5. Mp = 86–89 °C; $[\alpha]_D^{22} = +39.1$ (*c* 1.96, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.66; H, 8.93; N, 5.49.

4.5. Synthesis of 6, 7, *ent*-6 and *ent*-7 by selenocyclization

To a solution of *N*-(phenylseleno)phthalimide (1.4 mmol) in dichloromethane (6 mL) compounds **5** or *ent*-**5** (1 mmol) and a catalytic amount of $BF_3{\cdot}Et_2O$ were added at 0 °C. The temperature was allowed to raise to room temperature and the progress of the reaction was monitored by TLC. When the starting products **5** or *ent*-**5** were consumed an excess of $BF_3{\cdot}Et_2O$ was added to carry out the cleavage of the *N*-Boc bond. The reaction mixture was then poured into a 5% aqueous solution of NaOH and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered and evaporated. 2-Phenyl-5-[(phenylseleno)methyl]pyrrolidines **6**, **7**, *ent*-**6** and *ent*-**7** were separated by flash chromatography (diethyl ether/light petroleum from 5:95 to 20:80 as eluant). The physical and spectral data are reported below.

4.5.1. (2*S*,5*R*)-2-Phenyl-5-[(phenylseleno)methyl pyrrolidine, 6. Oil; $[\alpha]_D^{21} = -89.1$ (*c* 2.86, $CHCl_3$). ^1H NMR: δ 7.55–7.50 (m, 2H), 7.48–7.25 (m, 8H), 4.21 (dd, 1H, $J = 7.0$, 7.2 Hz), 3.54 (quint, 1H, $J = 6.9$ Hz), 3.20 (dd, 1H, $J = 5.7$, 12.0 Hz), 3.12 (dd, 1H, $J = 6.8$, 12.0 Hz), 2.25–2.14 (m, 2H), 2.07–2.00 (m, 1H), 1.81–1.66 (m, 2H); ^{13}C NMR: δ 144.7, 132.8 (two carbons), 130.6, 129.0 (two carbons), 128.2 (two carbons), 126.8, 126.7, 126.5 (two carbons), 62.4, 58.2, 35.2, 34.3, 31.4; MS *m*/*z* (rel int.): 317 (4), 172 (39), 146 (100), 129 (68), 104 (12), 91 (20), 77(16). Anal. Calcd for $C_{17}H_{19}NSe$: C, 64.55; H, 6.05; N, 4.43. Found: C, 64.57; H, 6.12; N, 4.58.

4.5.2. (2*R*,5*S*)-2-Phenyl-5-[(phenylseleno)methyl pyrrolidine, *ent*-6. Oil; $[\alpha]_D^{24} = +86.3$ (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NSe$: C, 64.55; H, 6.05; N, 4.43. Found: C, 64.61; H, 6.18; N, 4.53.

4.5.3. (2*S*,5*S*)-2-Phenyl-5-[(phenylseleno)methyl]pyrrolidine, 7. Oil; $[\alpha]_D^{22} = +1.4$ (*c* 2.34, $CHCl_3$); ^1H NMR: δ 7.75–7.68 (m, 2H), 7.30–7.20 (m, 8H), 4.35 (dd, 1H, $J = 6.9$, 7.2 Hz), 3.70 (quint, 1H, $J = 6.7$ Hz), 3.12 (dd, 1H, $J = 6.2$, 12.0 Hz), 3.08 (dd, 1H, $J = 7.0$, 12.0 Hz), 2.37–2.25 (m, 1H), 2.25–2.14 (m, 2H), 1.85–1.75 (m, 1H), 1.66 (dddd, 1H, $J = 6.6$, 7.7, 9.0, 12.3 Hz); ^{13}C NMR: δ 145.2, 132.8 (two carbons), 130.0, 129.1 (two carbons), 128.4 (two carbons), 126.9, 126.8, 126.3 (two carbons), 61.2, 57.9, 35.4, 35.0, 32.3; MS *m*/*z* (rel int.): 317 (4), 172 (38), 146 (100), 129 (67), 117 (18), 104 (12), 91 (21), 77 (16). Anal. Calcd for $C_{17}H_{19}NSe$: C, 64.55; H, 6.05; N, 4.43. Found: C, 64.63; H, 6.15; N, 4.39.

4.5.4. (2*R*,5*R*)-2-Phenyl-5-[(phenylseleno)methyl]pyrrolidine, *ent*-7. Oil; $[\alpha]_D^{24} = -1.0$ (*c* 2.1, $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NSe$: C, 64,55; H, 6,05; N, 4,43. Found: C, 64,59; H, 6,11; N, 4,38.

4.6. Synthesis of 8, *ent*-8, 9 and *ent*-9 by reductive deselenenylation

To a solution of compounds **6**, **7**, *ent*-**6** or *ent*-**7** (0.3 mmol) in dry benzene (3 mL) triphenyltin hydride (0.5 mmol) and a catalytic amount of AIBN were added and the mixture was stirred and refluxed for 1 h. The solvent was then removed under reduced pressure. The deselenenylated products **8**, **9**, *ent*-**8** and *ent*-**9** were isolated after a simple filtration on a deactivated silica gel column using a 10:90 mixture of ethyl ether and light petroleum as the eluant. Deactivated silica gel was prepared[5c] by washing silica gel with a 5% suspension of $NaHCO_3$ in methanol and then by filtering and drying in an oven at 150 °C. The products obtained and the reactions yields are reported in Schemes 1 and 3. Physical and spectral data of compounds **8** are reported in the literature,[5c] while those of compounds **9** and *ent*-**9** are reported below.

4.6.1. (2*R*,5*R*)-2-Methyl-5-phenylpyrrolidine, *ent*-8. Oil; $[\alpha]_D^{22} = +33.6$ (*c* 2.12, CH_2Cl_2). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 82.07; H, 9.22; N, 8.75.

4.6.2. (2*R*,5*S*)-2-Methyl-5-phenylpyrrolidine, 9. Oil; $[\alpha]_D^{25} = -19.8$ (*c* 0.92, CH_2Cl_2). ^{1}H NMR: δ 7.35–7.29 (m, 2H), 7.28–7.15 (m, 3H), 4.38 (dd, 1H, $J = 7.3$, 7.6 Hz), 4.12 (br s, 1H), 3.57 (sex, 1H, $J = 6.4$ Hz), 2.29–2.21 (m, 1H), 2.13–2.05 (m, 1H), 1.89–1.79 (m, 1H), 1.52–1.42 (m, 1H), 1.20 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR: δ 145.7, 128.5 (two carbons), 127.4, 126.8 (two carbons), 61.7, 54.8, 34.4, 34.0, 20.8; MS *m*/*z* (rel int.): 161 (3), 160 (29), 159 (100), 144 (55), 131 (76), 117 (38), 104 (88), 73 (66). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.97; H, 9.50; N, 8.78.

4.6.3. (2*S*,5*R*)-2-Methyl-5-phenylpyrrolidine, *ent*-9. Oil; $[\alpha]_D^{25} = +19.8$ (*c* 1.06, CH_2Cl_2). Anal. Calcd for $C_{11}H_{15}N$: C, 81,94; H, 9,38; N, 8,69. Found: C, 81,99; H, 9,43; N, 8,81.

4.7. Synthesis of 10, *ent*-10, 11 and *ent*-11 by *one-pot* reductive deselenenylation and *N*-Boc-protections

The syntheses of these compounds were effected in *one pot* by deselenenylation followed by protection. The deselenylation reaction was carried out as described above. After 3 h, the reaction mixtures were allowed to cool to room temperature and di-*tert*-butyl dicarbonate (0.6 mmol) and triethylamine (0.6 mol) were added. The mixtures were stirred overnight. The solvent was removed under vacuum, and the residues were chromatographed on silica gel using a 10:90 mixture of diethyl ether and light petroleum as eluant. Spectral data of compound **10** as 93:7 diastereomeric mixture are reported in the literature[5e] while those of compounds **11** and *ent*-**11** are reported below. The enantiomeric purity (99:1) of *cis* pyrrolidines **10** (t_R 5.5 min) and *ent*-**10** (t_R 8.2 min) was determined by HPLC on a (*R*,*R*)-Whelk-O 1 column (250 × 4 mm), using a mixture of *i*-PrOH/hexane (1:99), flow rate 1ml/min, UV detection at 220 nm. The enantiomeric purity (99:1) of *trans* pyrrolidines **11** (t_R 6.9 min) and *ent*-**11** (t_R 6.4 min) was determined using a Chiracel OD-H column (250 × 4 mm, Daicel), eluant *i*-PrOH/hexane (0.6:99.4), flow rate 1 mL/min, UV detection at 220 nm.

4.7.1. *tert*-Butyl (2*S*,5*S*)-2-methyl-5-phenylpyrrolidine-1-carboxylate, 10.[5e]. Oil; $[\alpha]_D^{23} = -35.9$ (*c* 1.53, CH_2Cl_2). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.76; N, 5.42.

4.7.2. *tert*-Butyl (2*R*,5*R*)-2-methyl-5-phenylpyrrolidine-1-carboxylate, *ent*-10. Oil; $[\alpha]_D^{23} = +36.4$ (*c* 2.54, CH_2Cl_2). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.59; H, 8.96; N, 5.46.

4.7.3. *tert*-Butyl (2*R*,5*S*)-2-methyl-5-phenylpyrrolidine-1-carboxylate, 11. Mp = 65–67 °C; $[\alpha]_D^{28} = -92.0$ (*c* 2.69, $CHCl_3$); *Major conformer* ^{1}H NMR: δ 7.28–7.01 (m, 5H), 4.86 (d, 1H, $J = 8.3$ Hz), 4.33–4.27 (m, 1H), 2.49–2.36 (m, 1H), 2.20–2.06 (m, 1H), 1.79–1.63 (m, 1H), 1.54–1.48 (m, 1H), 1.30 (d, 3H, $J = 6.2$ Hz), 1.15 (s, 9H); ^{13}C NMR: δ 146.7, 139.0, 128.0 (two carbons), 126.3, 125.3 (two carbons), 78.9, 61.7, 53.8, 32.5, 29.1, 28.1 (three carbons), 19.9. *Minor conformer* (*distinct signals*): ^{1}H NMR: δ 5.02 (d, 1H, $J = 8.2$ Hz), 1.48 (s, 9H), 1.28 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR: δ 145.4, 138.6 128.3 (two carbons), 126.4, 125.1 (two carbons), 79.0, 61.0, 53.8, 31.8, 29.8, 28.5 (three carbons), 20.7; MS *m*/*z* (rel int.): 261 (2), 205 (100), 190 (59), 160 (62), 146 (77), 133 (34), 117 (22), 104 (18), 91 (20), 77 (14), 57 (66). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.96; N, 5.41.

4.7.4. *tert*-Butyl (2*S*,5*R*)-2-methyl-5-phenylpyrrolidine-1-carboxylate, *ent*-11. Mp = 65–70 °C; $[\alpha]_D^{28} = +88.6$ (*c* 2.19, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C,73.61; H, 8.96; N, 5.27.

4.8. Substitution reactions of selenone 14

Selenide **13** (Scheme 4) was oxidized to selenone **14** with Oxone® according to the mild procedure described in the literature.[19] The progress of the reaction was followed by TLC. When the selenide and the selenoxide had disappeared, the reaction mixture was poured into water and extracted with dichloromethane. The solvent was evaporated and the crude selenone **14** (70% yield) was obtained. TLC analysis indicated that the product was sufficiently pure to be used without further purification. The experimental conditions employed to effect the displacement of the selenonyl group are reported in Table 1. With the exception of the reaction with sodium iodide in which the solvent was removed under reduced pressure, the other reaction mixtures were poured into water and extracted with diethyl ether. The organic layers were washed with water and with brine, dried over Na_2SO_4, filtered and evaporated under vacuum. Reaction products **15a–d** were obtained in a pure form after column chromatography of the residue on silica gel with a mixture of diethyl ether and light petroleum (from 5:95 to 20:80) as eluant. The physical and spectral data of compound **15d** have already been described in the literature.[21] Those of compounds **15a–c** are reported below.

4.8.1. *tert*-Butyl (2*S*)-2-(azidomethyl)pyrrolidine-1-carboxylate, 15a. Oil; $[\alpha]_D^{25} = -47.4$ (*c* 2.19, $CHCl_3$);[22] ^{1}H NMR (325 K): δ 3.99–3.92 (m, 1H), 3.59–3.33 (m, 4H), 2.16–1.76 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (325 K): δ 154.4, 79.7, 56.6, 53.5, 46.9, 29.1, 28.5 (three carbons), 23.5; MS *m*/*z* (rel int.): 226 (M^+ <1%), 170 (30), 114 (88), 70 (97), 57 (100); FT-IR (HATAR): 2095 cm^{-1} (N_3), 1693 cm^{-1} (CO) Anal. Calcd for $C_{10}H_{18}N_4O_2$: C, 53.08; H, 8.02; N, 24.76. Found: C, 53.16; H, 8.11; N, 24.84.

4.8.2. *tert*-Butyl (2*S*)-2-(cyanomethyl)pyrrolidine-1-carboxylate, 15b. Oil; $[\alpha]_D^{22} = -87.7$ (*c* 1.83, $CHCl_3$); ^{1}H NMR (325 K): δ 4.02–3.99 (m, 1H), 3.50–3.33 (m, 2H), 2.76–2.63 (m, 2H), 2.25–2.12 (m, 1H), 2.09–1.77 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (325 K): δ 154.5, 117.5, 80.1, 53.9, 47.0, 29.6, 28.5 (three carbons), 23.4, 22.7; MS *m*/*z* (rel int.): 210 (M^+ <1%), 170 (59), 137 (100), 114 (45), 70 (86), 57 (74); FT-IR (HATAR): 2243

cm^{-1} CN, 1694 cm^{-1} CO. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.85; H, 8.78; N, 13.44.

4.8.3. *tert*-Butyl (2*S*)-2-[(methylthio)methyl]pyrrolidine-1-carboxylate, 15c. Oil; $[\alpha]_D^{20} = -51.7$ (*c* 1.90, $CHCl_3$); ^1H NMR (325 K): δ 4.02–3.92 (m, 1H), 3.45–3.32 (m, 2H), 2.88–2.83 (m, 1H), 2.51–2.47 (m, 1H), 2.15 (s, 3H), 2.05–1.78 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (325 K): δ 154.3, 79.2, 56.8, 46.8, 38.0, 30.0, 28.5 (three carbons), 23.2, 15.8; MS *m*/*z* (rel int.): 231 (8), 170 (91), 158 (53), 130 (16), 114 (99), 70 (100), 57 (85). Anal. Calcd for $C_{11}H_{21}NO_2S$: C, 57.11; H, 9.15; N, 6.05. Found: C, 57.23; H, 9.27; N, 6.16.

4.9. Substitution reactions of selenone 17

Selenone **17** (Scheme 5) was obtained by oxidation of selenide **16** following the same procedure described above for compound **14**. The crude selenone was used without further purification. The experimental conditions employed to effect the displacement of the selenonyl group are reported in Table 2. After the usual workup, products **20a–d** were obtained in a pure form by column chromatography of the residue on silica gel with a mixture of diethyl ether and light petroleum (from 5:95 to 20:80) as eluant. Compound **20c** was accompanied by the N–H derivative **20c′**. The physical and spectral data of compounds **20a–d** and **20c′** are reported below.

4.9.1. *tert*-Butyl (2*R*,5*S*)-2-(azidomethyl)-5-phenylpyrrolidine-1-carboxylate, 20a. Oil; $[\alpha]_D^{23} = -37.3$ (*c* 1.78, $CHCl_3$); ^1H NMR (325 K): δ 7.33–7.12 (m, 5H), 4.80 (dd, 1H, $J = 6.7$, 7.1Hz), 4.16–4.08 (m, 1H), 3.78 (dd, 1H, $J = 3.8$, 12.0 Hz), 3.47 (dd, 1H, $J = 8.1$, 12.0 Hz), 2.32–2.24 (m, 1H), 2.12–2.02 (m, 1H), 1.99–1.86 (m, 2H), 1.29 (s, 9H); ^{13}C NMR (325 K): δ 154.9, 144.0, 128.2 (two carbons), 126.6, 125.6 (two carbons), 79.9, 63.0, 58.4, 54.3, 33.9, 28.1 (three carbons), 28.0; MS *m*/*z* (rel int.): 246 (57), 190 (85), 146 (100), 129 (69), 57 (71); FT-IR (HATAR): 2098 cm^{-1} (N_3), 1693 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.62; H, 7.41; N, 18.65.

4.9.2. *tert*-Butyl (2*R*,5*S*)-2-(2-cyanomethyl)-5-phenylpyrrolidine-1-carboxylate, 20b. Oil; $[\alpha]_D^{26} = +12.5$ (*c* 2.10, $CHCl_3$); ^1H NMR (315 K): δ 7.34–7.21 (m, 5H), 4.81 (dd, 1H, $J = 6.3$, 6.5 Hz), 4.25–4.19 (m, 1H), 3.04 (dd, 1H, $J = 4.0$, 16.6 Hz), 2.73 (dd, 1H, $J = 8.3$, 16.4 Hz), 2.37–2.18 (m, 2H), 2.07–1.93 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (315 K): δ 154.9, 143.4, 128.4 (two carbons), 126.9, 126.6 (two carbons), 117.7, 80.5, 63.3, 55.7, 33.9, 29.7, 28.1 (three carbons), 23.4; MS *m*/*z* (rel int.): 287 (M^+ <1%), 230 (92), 213 (41), 185 (57), 146 (100), 129 (51), 57 (63); FT-IR (HATAR): 2248 cm^{-1} (CN), 1692 cm^{-1} (CO). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.28; H, 7.62; N, 9.66.

4.9.3. *tert*-Butyl (2*R*,5*S*)-2-[(methylthio)methyl]-5-phenylpyrrolidine-1-carboxylate, 20c. Mp = 86–90 °C $[\alpha]_D^{29} = -19.6$ (*c* 1.65, $CHCl_3$); ^1H NMR (315 K): δ 7.33–7.17 (m, 5H), 4.85–4.75 (m, 1H), 4.21–4.14 (m, 1H), 3.16 (dd, 1H, $J = 2.3$, 12.8 Hz), 2.57 (dd, 1H, $J = 10.6$, 12.7 Hz), 2.34–2.21 (m, 1H), 2.22 (s, 3H), 2.15–2.04 (m, 1H), 2.01–1.83 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (315 K): δ 154.8, 143.1, 128.2 (two carbons), 126.5, 125.5 (two carbons), 79.6, 63.1, 58.6, 38.6, 34.2, 29.0, 28.3 (three carbons), 15.8; MS *m*/*z* (rel int.): 307 (M^+ <1%), 246 (63), 190 (63), 146 (100), 129 (40), 57 (41). Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.53; H, 8.26; N, 4.68.

4.9.4. (2*R*,5*S*)-2-[(Methylthio)methyl]-5-phenylpyrrolidine, 20c′. Oil; $[\alpha]_D^{29} = -69.9$ (*c* 0.69, $CHCl_3$); ^1H NMR: δ 7.41–7.18 (m, 5H), 4.21(dd, 1H, $J = 7.7$, 7.9 Hz), 3.47 (quint, 1H, $J = 7.0$ Hz), 2.72 (dd, 1H, $J = 5.8$, 12.9 Hz), 2.68 (dd, 1H, $J = 5.9$, 12.9 Hz), 2.18 (s, 3H), 2.10–1.60 (m, 5H); ^{13}C NMR: δ 144.2, 128.3 (two carbons), 126.9, 125.5 (two carbons), 62.4, 57.9, 40.8, 33.8, 30.8, 16.2; MS *m*/*z* (rel int.): 207 (1), 146 (100), 129 (56), 91 (6), 77 (4). Anal. Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76. Found: C, 69.63; H, 8.38; N, 6.64.

4.9.5. *tert*-Butyl (2*R*,5*S*)-2-(iodomethyl)-5-phenylpyrrolidine-1-carboxylate, 20d. Oil; $[\alpha]_D^{26} = -25.2$ (*c* 1.60, $CHCl_3$); ^1H NMR (315 K): δ 7.32–7.20 (m, 5H), 4.86–4.83 (m, 1H), 4.28–4.24 (m, 1H), 3.82–3.76 (m, 1H), 3.16 (dd, 1H, $J = 9.7$, 9.9 Hz), 2.33–2.24 (m, 1H), 2.22–2.12 (m, 1H), 2.01–1.89 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (315 K): δ 154.7, 143.8, 128.3 (two carbons), 126.7, 125.5 (two carbons), 80.1, 63.8, 60.8, 33.9, 30.2, 28.2 (three carbons), 8.9; MS *m*/*z* (rel int.): 387 (M^+ <1%), 331 (98), 246 (40), 190 (73), 146 (100), 57 (66). Anal. Calcd for $C_{16}H_{22}INO_2$: C, 49.62; H, 5.73; N, 3.62. Found: C, 49.59; H, 5.85; N, 3.74.

4.10. Substitution reactions of selenone 19

Selenone **19** (Scheme 5) was obtained by oxidation of selenide **18** following the same procedure described above for compound **14**. In this case, however, 3 M equiv of Oxone® was necessary and the reaction mixture was stirred for 6 h at 80 °C. The crude selenone was used without further purification. The experimental conditions employed to effect the displacement of the selenonyl group are reported in Table 3. After the usual workup, products **21a–c** were obtained in a pure form by column chromatography of the residue on silica gel using a mixture of diethyl ether and light petroleum (from 50:50 to 90:10) as eluant. In the cases of the reactions with sodium azide and potassium cyanide the substitution products **21b** and **21c** were accompanied by the elimination derivatives **21b′** and **21c′**. The physical and spectral data of compounds **21a–c**, **21b′** and **21c′** are reported below.

4.10.1. (2*S*,5*S*)-2-(Azidomethyl)-5-phenylpyrrolidine, 21a. Oil; $[\alpha]_D^{23} = -31.0$ (*c* 1.87, $CHCl_3$); ^1H NMR: δ 7.35–7.23 (m, 5H), 4.30 (dd, 1H, $J = 6.5$, 8.0 Hz), 3.67 (dq, 1H, $J = 5.2$, 7.0 Hz), 3.35 (dd, 1H, $J = 5.7$, 12.0 Hz), 3.30 (dd, 1H, $J = 7.1$, 12.0 Hz), 2.32–2.24 (m, 1H), 2.17–2.08 (m, 1H), 2.06 (br s, 1H), 1.84–1.74 (m, 1H), 1.65–1.56 (m, 1H); ^{13}C NMR: δ 144.6, 128.4 (two carbons), 126.9, 126.2 (two carbons), 61.6, 57.6, 56.5, 34.8, 29.5; MS *m*/*z* (rel int.): 202 (M^+ <1%), 146 (100), 129 (64), 117 (20),

91 (11), 77(3); FT-IR (HATAR): 2091 cm^{-1} (N_3). Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.44; H, 6.86; N, 27.82.

4.10.2. (2*S*)-2-(Azidomethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole, 21a′. Oil; $[\alpha]_D^{24} = +38.4$ (*c* 0.69, $CHCl_3$); ^1H NMR: δ 7.87–7.84 (m, 2H), 7.48–7.40 (m, 3H), 4.51–4.42 (m, 1H), 3.63 (dd, 1H, $J = 7.1$, 12.4 Hz), 3.51 (dd, 1H, $J = 5.2$, 12.3 Hz), 3.12 (dddd, 1H, $J = 2.2$, 4.9, 10.1, 12.3 Hz), 2.98 (dddd, 1H, $J = 1.7$, 7.3, 9.8, 12.3 Hz), 2.24 (dddd, 1H, $J = 4.9$, 8.1, 9.8, 13.5 Hz), 1.83 (dddd, 1H, $J = 7.3$, 7.5, 10.1, 13.5 Hz); ^{13}C NMR: δ 174.5, 134.1, 130.7, 128.4 (two carbons), 127.8 (two carbons), 72.7, 55.7, 35.4, 25.9; MS *m*/*z* (rel int.): 200 (M^+ <1%), 144 (100), 115 (44), 91 (58), 77 (20); FT-IR (HATAR): 2096 cm^{-1} N_3. Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.96; H, 6.12; N, 27.86.

4.10.3. [(2*S*,5*S*)-5-Phenylpyrrolidin-2-yl]acetonitrile, 21b. Oil; $[\alpha]_D^{25} = -20.3$ (*c* 0.60, $CHCl_3$); ^1H NMR: δ 7.37–7.24 (m, 5H), 4.40 (dd, 1H, $J = 6.6$, 7.0 Hz), 3.82 (quint, 1H, $J = 6.6$ Hz), 2.55–2.51 (m, 2H), 2.39–2.21 (m, 2H), 1.99 (br s, 1H), 1.90–1.79 (m, 1H), 1.75–1.66 (m, 1H); ^{13}C NMR: δ 144.2, 128.6 (two carbons), 127.2, 126.2 (two carbons), 118.5, 61.9, 54.6, 34.6, 31.8, 25.4; MS *m*/*z* (rel int.): 186 (5), 185 (17), 146 (100), 129 (49),117 (19), 104 (14), 91 (11); FT-IR (HATAR): 2246 cm^{-1} CN. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.45; H, 7.49; N, 15.18.

4.10.4. [(2*S*)-5-Phenyl-3,4-dihydro-2*H*-pyrrol-2-yl]acetonitrile, 21b′. Oil; slightly impure [α] not determined; ^1H NMR: δ 7.86–7.84 (m, 2H), 7.50–7.39 (m, 3H), 4.55–4.45 (m, 1H), 3.20 (dddd, 1H, $J = 2.2$, 4.6, 10.1, 14.6 Hz), 3.02 (dddd, 1H, $J = 1.8$, 7.6, 9.5, 14.6 Hz), 2.84 (dd, 1H, $J = 5.1$, 16.6 Hz), 2.77 (dd, 1H, $J = 6.8$, 16.7 Hz), 2.40 (dddd, 1H, $J = 4.5$, 7.9, 9.9, 12.6 Hz), 1.84 (dddd, 1H, $J = 6.8$, 7.1, 10.0, 12.6 Hz); ^{13}C NMR: δ 174.5, 133.6, 131.0, 128.5 (two carbons), 127.8 (two carbons), 117.9, 68.5, 35.6, 27.9, 24.6. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.35; H, 6.69; N, 15.33.

4.10.5. (2*S*,5*S*)-2-[(Methylthio)methyl]-5-phenylpyrrolidine, 21c. Oil; $[\alpha]_D^{28} = +26.6$ (*c* 1.37, $CHCl_3$); ^1H NMR: δ 7.40–7.20 (m, 5H), 4.30 (dd, 1H, $J = 6.7$, 7.0 Hz), 3.65 (quint, 1H, $J = 6.7$ Hz), 2.66–2.61 (m, 2H), 2.32–2.18 (m, 2H), 2.16 (s, 3H), 1.99 (br s, 1H), 1.84–1.74 (m, 1H), 1.68–1.57 (m, 1H); ^{13}C NMR: δ 145.1, 128.3 (two carbons), 126.8, 126.3 (two carbons), 60.9, 56.8, 40.9, 34.7, 31.5, 15.6; MS *m*/*z* (rel int.): 207 (M <1%), 206 (1), 146 (100), 129 (78), 91 (11), 77 (8). Anal. Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76. Found: C, 69.63; H, 8.37; N, 6.89.

Acknowledgements

Financial support from MIUR, National Projects PRIN2003, PRIN2005, FIRB2001 and Consorzio CINMPIS is gratefully acknowledged.

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