Stereocontrolled synthesis of substituted *N*-arenesulfonyl azetidines from γ-(phenylseleno)alkyl arylsulfonamides

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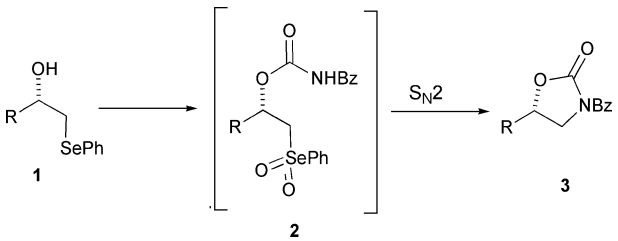
Received 21st August 2007, Accepted 5th September 2007
First published as an Advance Article on the web 21st September 2007
DOI: 10.1039/b712861d

Different synthetic methodologies for the stereocontrolled synthesis of substituted azetidines are reported. The approach utilizes an optimized oxidation reaction of γ-(phenylseleno)alkyl arylsulfonamides, followed by the intramolecular substitution of the resulting phenylselenonyl group by the nitrogen atom.

Introduction

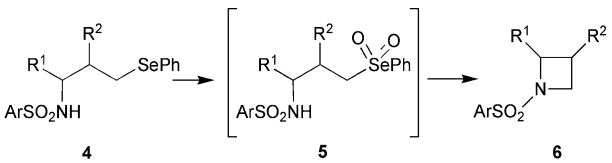
Azetidines are an interesting and important class of four-membered heterocyclic compounds because of their reactivity[1] and biological activity.[2] The formation of the azetidine ring from acyclic precursors is a disfavoured process compared to the analogous construction of six-, five- and even three-membered rings. Only a few stereospecific methods are available for their synthesis, especially in enantiomerically pure form. Optically active azetidines, which can find application in enantioselective catalysis,[3] are generally obtained from racemic mixtures using stoichiometric amounts of enantiomerically pure auxiliaries to form diastereoisomeric pairs.[4] Enzymatic resolutions have also been explored.[5] Some enantioselective syntheses of azetidines have also been reported. Interesting examples are the intermolecular reaction of chiral non-racemic 1,3-dihalo or 1,3-diol derivatives with primary amines,[6] the intramolecular cyclization of optically active 1,3-amino alcohols or 3-amino-1,2-diols,[7] the reduction of enantiomerically pure β-lactams[8] and the intramolecular alkylation of an α-amino stabilized carbanion obtained from optically pure β-amino alcohols.[9] Another approach is based on a two-step methodology involving an internal alkylation of a chiral non-racemic haloaminohydrin[10] followed by debenzylation of the resulting azetidinium salt. Enantiomerically pure 3-oxo-azetidines can be then prepared by diazoketones, derived from *N*-protected α-amino acids, through insertion of carbenoid species into the N–H bond.[11]

As part of our ongoing interest in the chemistry of organoselenium compounds we have recently observed that the selenonyl group can be easily intramolecularly displaced by nitrogen nucleophiles thus affording nitrogen containing heterocyclic compounds.[12] Thus, starting from chiral non-racemic β-hydroxyalkyl phenyl selenides **1** we effected the stereospecific synthesis of various substituted optically active 1,3-oxazolidin-2-ones **3**. As indicated in Scheme 1, compounds **1** were transformed into the corresponding *N*-benzoyl carbamate derivatives which were oxidized to selenones **2**.[13] These, in the presence of a base, gave the desired compounds **3**. The key step of the process is a new ring closure reaction which occurs by a stereospecific intramolecular nucleophilic substitution of the selenonyl group by the nitrogen atom of the carbamate.



Scheme 1 Synthesis of *N*-benzoyl-oxazolidin-2-ones from β-hydroxyalkyl phenyl selenides.

A similar reaction sequence is now described for a new and convenient stereospecific synthesis of substituted *N*-arenesulfonyl azetidines **6** starting from substituted γ-phenylseleno arylsulfonamides **4** which are oxidized to the selenones **5** and then cyclized (Scheme 2).



R^1= H, Me, Et, nPr, $CyCH_2$, Bn, CH_2OH, CO_2Me. R^2= H or OTHP
Ar = *o*-$O_2NC_6H_4$, *p*-MeC_6H_4

Scheme 2 Synthesis of azetidines **6** by intramolecular substitution of the selenonyl group by a nitrogen atom.

To our knowledge a similar intramolecular substitution has been reported only in one case, for the preparation of the unsubstituted *N*-tosyl azetidine (Scheme 2: $R^1 = R^2 = H$, Ar = *p*-Tol).[14] After this report no other examples have been described in the literature. One important step of our procedure is the preparation of the starting sulfonamides **4**, whose syntheses have not been reported in the literature so far. In the present paper we therefore describe some simple stereocontrolled methods to effect the synthesis of these interesting compounds.

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Results and discussion

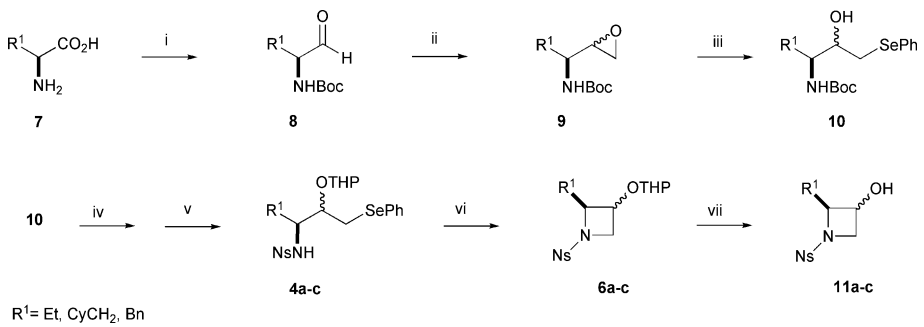
The required phenylseleno sulfonamides **4** were prepared by different synthetic approaches starting from commercially available chiral building blocks such as epoxides, lactones and esters or through enantioselective processes starting from achiral compounds.

Method 1: Preparation of γ-[*N*-(phenylseleno)alkyl]-arylsulfonamides 4a–c from α-amino epoxides

The first method uses as starting materials enantiomerically pure α-amino acids which were transformed into the corresponding α-amino epoxides. As depicted in Scheme 3 (*S*)-α-amino acids **7** were efficiently converted into the corresponding enantiopure *N*-Boc α-amino aldehydes **8** according to the procedures described in the literature.[15,16] These were treated with dimethyl sulfoxonium methylide, according to the procedure described by Ashton *et al.*,[17] to afford the epoxides **9a,b** as 4 : 1 *syn–anti* mixtures (as determined by ^{1}H NMR[15,16,18]) of two diastereoisomers which could not be separated. Regiospecific opening of these mixtures with phenylselenolate anions[12] provided the corresponding mixtures of the two β-hydroxyselenides **10a,b** in good yields. The β-hydroxyselenide **10c** was directly prepared from the commercially available enantiomerically enriched epoxide **9c** (98% ee). After deprotection of **10a–c** and reprotection of the amino group as 2-nitrobenzenesulfonyl (nosyl) derivatives, the intermediate alcohols were directly converted into the corresponding tetrahydropyranyl derivatives of substituted γ-[*N*-(phenylseleno) alkyl]arylsulfonamides **4a–c** (Scheme 3).

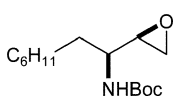
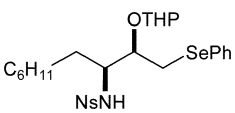
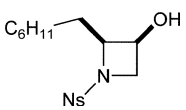
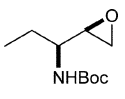
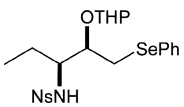
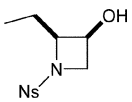
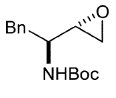
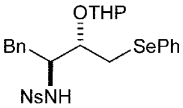
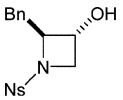
Cyclizations of γ-[*N*-(phenylseleno)alkyl]arylsulfonamides 4a–c to azetidines 6a–c

The oxidations of selenides **4a–c** into the selenones **5a–c** were carried out in THF at room temperature with an excess of *m*-chloroperoxybenzoic acid and in the presence of potassium hydrogenphosphate according to our previously reported method.[12] The selenone intermediates[19,20] were not isolated but directly cyclized to the azetidines **6a–c** by addition of powdered potassium hydroxide. After the usual workup, evaporation of the solvent afforded the crude *N*-nosyl azetidines **6a–c** which were finally deprotected to give the *N*-nosyl-3-azetidinols **11a–c** in satisfactory overall yields (Scheme 3 and Table 1).



Scheme 3 *Reagents and conditions*: (i) see ref. 16; (ii) $Me_3SO^+I^-$ (1.2 equiv.), NaH (1.1 equiv.), DMSO, 25 °C, 4 h; (iii) PhSeSePh (0.5 equiv.), $NaBH_4$ (1.0 equiv.), EtOH, 40 °C, 5 h; (iv) H_2SO_4 (10.0 equiv.), dioxane, 25 °C, 1 h; (v) NsCl (1.4 equiv.), Et_3N (1.4 equiv.), CH_2Cl_2, 0 °C → 25 °C, 14 h, then DHP (1.2 equiv.), TsOH·H_2O (0.01 equiv.), CH_2Cl_2, 25 °C, 20 h; (vi) MCPBA (4 equiv.), K_2HPO_4 (5 equiv.), THF, 25 °C, 3 h, then KOH (7.5 equiv.), 25 °C, 6 h; (vii) TsOH·H_2O (0.05 equiv.), MeOH, 25 °C, 16 h. Ns = 2-nitrobenzenesulfonyl; DHP = 3,4-dihydro-2*H*-pyran; MCPBA = 3-chloroperoxybenzoic acid; Ts = 4-toluenesulfonyl.

Table 1 Preparation of azetidine alcohols **11a–c** from α-amino epoxides **9**

Entry[a]	Epoxy amide **9**	*N*-Arylsulfonyl selenides **4**	Yields (%)[b]	Azetidines **11**	Yields (%)[c]
a			74		61
b			86		56
c			71		50

[a] The products reported in entries a and b are 4 : 1 mixtures of two diastereoisomers. Only the major diastereoisomer is indicated. [b] Yields calculated from the starting hydroxy selenides **10**. [c] Yields of the overall oxidation–cyclization–deprotection process.

Obviously the azetidine alcohols **11a** and **11b** were obtained as 4 : 1 mixtures of two diastereoisomers which could not be separated by column chromatography. Compound **11c** was instead obtained as a single enantiomer (98% ee). The nosyl group can be easily removed,[21] which increases the importance of the present method for the synthesis of optically active azetidines.

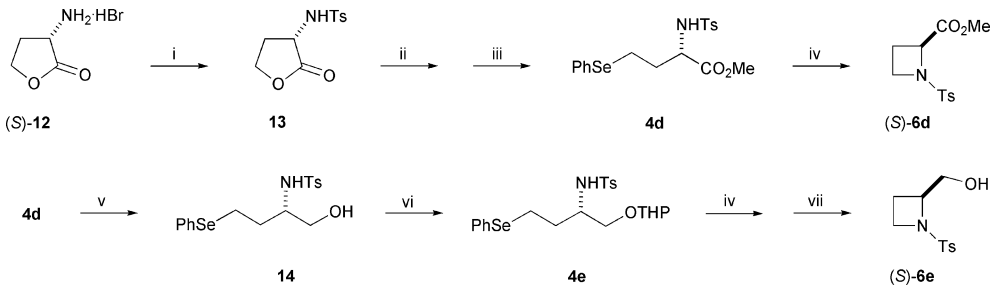
Method 2: Preparation of γ-[*N*-(phenylseleno) alkyl]arylsulfonamides 4d-f from γ-lactones and cyclization to azetidines 6d–f

The second synthetic approach to obtain the other sulfonamides necessary for the present investigation is indicated in Schemes 4 and 5.

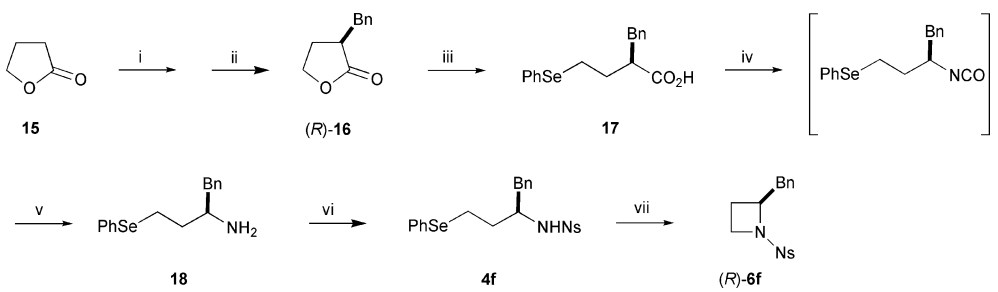
Enantiomerically enriched (98% ee) homoserine lactone hydrobromide **12** was protected as *N*-tosyl derivative **13** and then subjected to ring opening by phenylselenolate anion in DMF.[22] The resulting acid was directly treated with diazomethane to give the sulfonamide **4d**. After the oxidation–cyclization procedure shown above, the azetidine ester **6d** was obtained in moderate yield (44%). The physical properties of this compound were identical to those already described in the literature.[23] Compound **6d** is the precursor of L-azetidine-2-carboxylic acid (L-Aze) which, because of its constrained α-amino acid structure, has found many applications in pharmaceutical[24] and in synthetic chemistry.[25] The low yield of **6d** is probably due to the hydrolysis of the ester group by the hydroxide ion employed in the cyclization step. In fact, when the cyclization was performed on the tetrahydropyranyl derivative **4e**, synthesized from **4d** by reduction of the ester group, the known azetidine alcohol **6e**[23] was obtained in better yield (62%) (Scheme 4).

The simple γ-lactone **15** also can be employed as a precursor for a stereoselective synthesis of azetidines. Alkylation of **15** afforded the racemic α-benzyl-γ-lactone **16** (Scheme 5). The lithium enolate of **16** was enantioselectively protonated[26] with the chiral proton source *R*-pantolactone at −78 °C in THF. The optically active lactone **16** was obtained in a 61 : 39 enantiomeric ratio as determined by HPLC on a chiral stationary phase. The predominant *R* configuration was indicated by the sign of the specific optical rotation.[26] Compound **16** was then subjected to ring opening by phenylselenolate anion in DMF[22] to afford the acid **17**.

Through the simple steps described below, the acid **17** was transformed into the required γ-[*N*-(phenylseleno) alkyl]arylsulfonamide **4f**. Thus, the treatment of acid **17** with oxalyl chloride gave the crude acyl chloride which, with trimethylsilylazide in dichloromethane at 40 °C, afforded the corresponding isocyanate.[27] This was directly converted in good yield into the free amine **18**. Protection with 2-nitrobenzenesulfonyl chloride gave **4f** in good overall yield. The chiral non-racemic substituted *N*-nosylazetidine **6f** was then obtained in excellent yield after the usual oxidation–cyclization procedure. HPLC analysis on the chiral stationary phase of **6f** showed a 55 : 45 enantiomeric ratio indicating that a decrease in the enantiomeric ratio has occurred, probably during the Curtius rearrangement as previously observed.[28]



Scheme 4 *Reagents and conditions*: (i) TsCl (1.2 equiv.), Et_3N (2.2 equiv.), CH_2Cl_2, 0 °C → 25 °C, 7 h, 78%; (ii) PhSeSePh (0.5 equiv.), $NaBH_4$ (1.0 equiv.), DMF, 100 °C, 6 h; (iii) CH_2N_2, Et_2O, 25 °C, 5 min, 83% (two steps); (iv) MCPBA (4 equiv.), K_2HPO_4 (5 equiv.), THF, 25 °C, 2 h, then KOH (7.5 equiv.), 25 °C, 3 h, 44%; (v) $LiAlH_4$ (2.2 equiv.), THF, 0 °C, 2 h, 73%; (vi) DHP (2.0 equiv.), $TsOH·H_2O$ (0.1 equiv.), CH_2Cl_2, 25 °C, 18 h, 80%; (vii) $TsOH·H_2O$ (0.05 equiv.), MeOH, 25 °C, 8 h, 62% (two steps). Ts = 4-toluenesulfonyl; MCPBA = 3-chloroperoxybenzoic acid; DHP = 3,4-dihydro-2*H*-pyran.



Scheme 5 *Reagents and conditions*: (i) LDA (1.1 equiv.), THF, then BnBr (1.2 equiv.), −78 °C, 1 h, 70%; (ii) LDA (1.1 equiv.), THF, −78 °C, then (*R*)-(−)-pantolactone (2.0 equiv.), −78 °C, 10 min, 92%; (iii) PhSeSePh (0.5 equiv.), $NaBH_4$ (1 equiv.), DMF, 100 °C, 5 h, 75% (two steps); (iv) $(COCl)_2$ (1.5 equiv.), 25 °C, 5 h, then $TMSN_3$ (1.2 equiv.), CH_2Cl_2, 40 °C, 5 h; (v) 1 M aq. NaOH (1.1 equiv.), THF, 100 °C, 4 h; (vi) NsCl (1.3 equiv.), Et_3N (1.3 equiv.), CH_2Cl_2, 0 °C → 25 °C, 5 h, 55% (four steps); (vii) MCPBA (4 equiv.), K_2HPO_4 (5 equiv.), THF, 25 °C, 2 h, then KOH (7.5 equiv.), 25 °C, 15 h, 80%. $TMSN_3$ = trimethylsilylazide; Ns = 2-nitrobenzenesulfonyl; MCPBA = 3-chloroperoxybenzoic acid.

Method 3: Preparation of γ-[*N*-(phenylseleno) alkyl]arylsulfonamides 4g and 4h from γ-hydroxy selenides and cyclization to azetidines 6g and 6h

A simple substrate-controlled stereospecific synthesis of azetidines starting from easily available enantiomerically pure β-hydroxy esters is illustrated in Scheme 6. Thus commercial (*S*)-3-hydroxy ester **19** (98% ee) was easily converted in four steps (without isolation of the intermediates) into the γ-hydroxyselenide **20** in 71% overall yield. By reaction with phthalimide, under Mitsunobu conditions, **20** was converted into the corresponding phthalimido derivative. It is well known that the Mitsunobu reaction occurs with complete inversion of configuration at the stereogenic center.[29] Nitrogen deprotection of the crude phthalimide gave the corresponding free amine which was reacted with 2-nitrobenzenesulfonyl chloride to give the corresponding arylsulfonamide **4g** (71% yield). After the usual oxidation–cyclization procedure the optically active *N*-nosyl azetidine **6g** was obtained in good yield (59%). No loss of the enantiomeric purity occurred during all these conversions as demonstrated by the enantiomeric ratio of **6g** (>99 : 1), measured by HPLC analysis on the chiral stationary phase.

A different synthetic strategy for the preparation of optically active γ-hydroxyselenides is depicted in Scheme 7. Thus, the conjugate addition of benzeneselenol to the α,β-unsaturated ketone **21** gave the β-phenylseleno ketone **22** in excellent yield.[30] Asymmetric reduction with the reagent prepared from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol and borane[31] in THF produced the optically active γ-hydroxyselenide **23** in excellent yield but with low enantioselectivity. The enantiomerically enriched alcohol **23** was then converted into the arylsulfonamide **4h** through its corresponding phthalimide, as described above for the alcohol **20**.

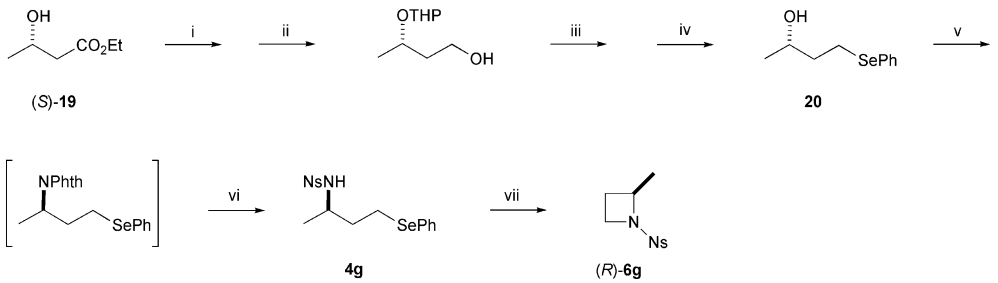
Finally oxidation of the selenium atom followed by addition of potassium hydroxide afforded the desired azetidine **6h** (70% yield) in 56 : 44 enantiomeric ratio as demonstrated by HPLC analysis.

Conclusions

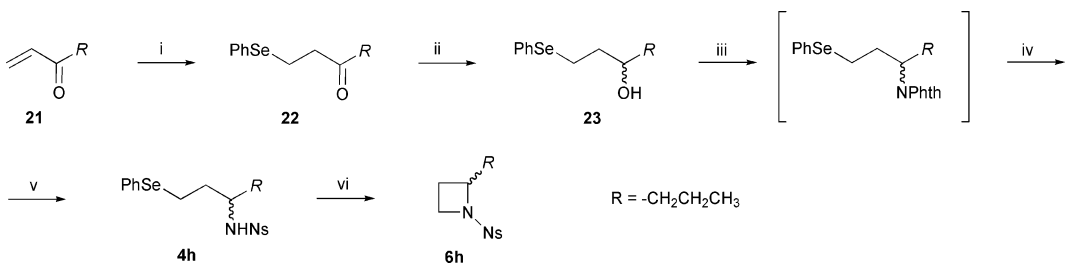
A new and convenient synthesis of substituted azetidines is presented. Different synthetic approaches to the γ-(phenylseleno)alkyl arylsulfonamides required as starting materials have also been developed. The key step in the formation of azetidines is the ring closure reaction which occurs by a stereospecific intramolecular nucleophilic substitution of the selenonyl group by the nitrogen atom of the arylsulfonamides. This reaction confirms the extremely good leaving ability of the selenonyl group. The present procedure favourably compares with other previously described methods. Preliminary results indicate that the procedure described here can also be applied to the synthesis of five- and six-membered ring heterocyclic compounds.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DR 200 at 200 and 50.3 MHz, respectively; unless otherwise specified, $CDCl_3$ was used as solvent. Chemical shifts



Scheme 6 *Reagents and conditions*: (i) DHP (1.2 equiv.), TsOH·H_2O (0.1 equiv.), Et_2O, 25 °C, 48 h; (ii) $LiAlH_4$ (2.2 equiv.), THF, 0 °C, 5 h; (iii) PhSeCN (1.2 equiv.), PBu_3 (1.2 equiv.), THF, 25 °C, 8 h; (iv) TsOH·H_2O (0.1 equiv.), MeOH, 25 °C, 18 h, 71% (four steps); (v) PPh_3 (1.4 equiv.), PhthNH (1.4 equiv.), DIAD (1.3 equiv.), THF, 0 °C → 25 °C, 7 h; (vi) H_2N–NH_2 (1.1 equiv.), EtOH, 110 °C, 2 h, then NsCl (1.4 equiv.), Et_3N (1.4 equiv.), CH_2Cl_2, 0 °C → 25 °C, 15 h, 71% (three steps); (vii) MCPBA (4 equiv.), K_2HPO_4 (5 equiv.), THF, 25 °C, 2 h, then KOH (7.5 equiv.), 6 h, 59%. DHP = 3,4-dihydro-2*H*-pyran; Ts = 4-toluenesulfonyl; PhthNH = phthalimide; DIAD = diisopropyl azodicarboxylate; Ns = 2-nitrobenzenesulfonyl; MCPBA = 3-chloroperoxybenzoic acid.



Scheme 7 *Reagents and conditions*: (i) PhSeSePh (0.6 equiv.), $NaBH_4$ (1.3 equiv.), EtOH, 25 °C, 3 h, 86%; (ii) 1 M BH_3 in THF (2.0 equiv.), (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (1.0 equiv.), 25 °C, 48 h, 87%; (iii) PPh_3 (1.4 equiv.), PhthNH (1.4 equiv.), DIAD (1.3 equiv.), THF, 0 °C → 25 °C, 14 h; (iv) H_2N–NH_2 (1.1 equiv.), EtOH, 110 °C, 3 h; (v) NsCl (1.4 equiv.), Et_3N (1.4 equiv.), CH_2Cl_2, 0 °C → 25 °C, 12 h, 66% (three steps); (vi) MCPBA (4 equiv.), K_2HPO_4 (5 equiv.), THF, 25 °C, 2 h, then KOH (7.5 equiv.), 5 h, 70%. PhthNH = phthalimide; DIAD = diisopropyl azodicarboxylate; Ns = 2-nitrobenzenesulfonyl; MCPBA = 3-chloroperoxybenzoic acid.

(δ) are reported in parts per million (ppm) and are referenced to tetramethylsilane (Me_4Si) for ^1H NMR or to the appropriate solvent peak (^{13}C NMR). Coupling constants (J) are quoted in Hertz (Hz) to the nearest 0.1 Hz. FT-IR spectra were recorded with a Jasco model 410 spectrometer on a Diffuse Reflectance sampling cell. Only significant absorption maxima (ν_{max}) are reported, and all absorptions are reported in wavenumbers (cm^{-1}). GC-MS analyses were obtained with a HP-6890 gas chromatograph (HP-5MS capillary column; 30 m × 0.25 mm i.d., film 0.25 μm) equipped with a HP-5973 mass selective detector at an ionizing voltage of 70 eV. For the ions containing selenium only the peaks arising from the selenium-80 isotope are given. HPLC was carried out using a HP 1100 system equipped with a UV/Vis detector with the columns and solvents specified. Melting points are uncorrected. Optical rotations were measured in a 50 mm cell with a Jasco DIP-1000 digital polarimeter using the D-line of sodium at the given temperature. $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g 100 mL^{-1}. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer. Commercial grade Et_2O and CH_2Cl_2 were used without purification. DMF, MeOH and EtOH were dried by using standard procedures. Reactions were monitored by thin layer chromatography (TLC) carried out on aluminium foil sheets pre-coated with silica (Merck silica gel 60 F_{254}), which were visualized by the quenching of UV fluorescence (λ_{max}254 nm) and/or by staining with 5% w/v phosphomolybdic acid in EtOH followed by heating. Column chromatography was performed on Merck silica gel 60 (70–230 mesh).

The optically active epoxide **9c**, the amino γ-lactone **12** and the β-hydroxy ester **19**, used as starting materials, were commercially available and have enantiomeric excesses equal to or greater than 98%. The analytical data for compounds **10a**,[12] **13**,[32] **6d**,[23] **6e**,[23] **16**,[33] and **20**[34] were in agreement with those already reported in the literature.

Caution

Because of their potentially explosive properties, all reactions involving azides were carried out with the appropriate protection under a well-ventilated hood.

Preparation of the epoxides 9a and 9b

The α-amino aldehydes **8a** and **8b** were obtained from the corresponding L-amino acids as reported by Luly *et al.*[16] and directly transformed into the epoxides **9a** and **9b** according to the procedure reported in the literature.[17] Epoxide **9a** was not isolated but it was directly transformed into the corresponding β-hydroxyalkyl phenyl selenide **10a**.

***tert*-Butyl (1*S*)-1-[(2*R*)-oxiran-2-yl]propylcarbamate and *tert*-butyl (1*S*)-1-[(2*S*)-oxiran-2-yl]propylcarbamate (9b).** (1.8 g, 61%). Pale yellow oil (found: C, 59.3; H, 9.75; N, 6.6. Calc. for $C_{10}H_{19}NO_3$: C, 59.6; H, 9.5; N, 6.9%); mixture of diastereoisomers *syn–anti* (83 : 17). *syn* Isomer (1*S*,2*R*): δ_H(200 MHz, $CDCl_3$, Me_4Si) 4.52 (1 H, d, J 8.5, N*H*), 3.88–3.70 (1 H, m, C*H*O), 3.07–2.98 (1 H, m, CH_2O), 2.92–2.69 (m, 1 H, CH_2O), 2.64–2.55 (1 H, m, C*H*N), 1.80–1.48 (2 H, m, CH_2), 1.46 (3 H, s, CH_3), 1.44 (6 H, s, 2 × CH_3) and 1.02 (3 H, t, J 7.5, CH_3); δ_C(50.3 MHz, $CDCl_3$) 155.7, 79.2, 53.2, 49.5, 44.0, 28.2 (3 C), 26.3, and 10.2; *anti* isomer (1*S*,2*S*) (distinct signals): δ_H 4.64 (1 H, d, J 8.5, N*H*), 3.42–3.23 (1 H, m, C*H*O) and 0.98 (3 H, t, J 7.5, CH_3); δ_C 155.5, 53.8, 45.9 and 9.9; *m*/*z* (E/I) 172 (13, M − CH_3CH_2), 158 (9%), 102 (16), 72 (36), 59 (23) and 57 (100).

Preparation of β-hydroxyalkyl phenyl selenides 10a–c

The β-hydroxyalkyl phenyl selenides **10a–c** were prepared by the regiospecific ring opening of the corresponding epoxides with sodium phenyl selenolate in ethanol as reported in the literature.[12] Yields, physical and spectral data are reported below.

***tert*-Butyl (1*S*,2*R*) and (1*S*,2*S*)-1-(cyclohexylmethyl)-2-hydroxy-3-(phenylseleno)propylcarbamate (10a),[12].** (1.6 g, 19% global yield starting from the corresponding amino acids). 82 : 18 mixture of *syn–anti* diastereoisomers as determined by ^1H NMR analysis.

***tert*-Butyl (1*S*,2*R*) and (1*S*,2*S*)-1-ethyl-2-hydroxy-3-(phenylseleno)propylcarbamate (10b).** (3.5 g, 97%). Yellow oil (found: C, 53.3; H, 7.3; N, 4.3. Calc. for $C_{16}H_{25}NO_3Se$: C, 53.6; H, 7.0; N, 3.9%); mixture of diastereoisomers *syn–anti* (83 : 17). *syn* Isomer: δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.60–7.42 (2 H, m, Ar*H*), 7.32–7.20 (3 H, m, Ar*H*), 4.75 (1 H, d, J 9.3, N*H*), 3.74–3.35 (2 H, m, C*H*O and C*H*N), 3.12 (1 H, dd, J 12.9 and 3.8, CH_2SeAr), 2.93 (1 H, dd, J 12.9, 9.5, CH_2SeAr), 2.84 (1 H, d, J 2.9, O*H*), 1.70–1.45 (2 H, m, CH_2CH$_3$), 1.43 (9 H, s, 3 × CH_3) and 0.91 (3 H, t, J 6.9, CH$_2$CH_3); δ_C(50.3 MHz, $CDCl_3$) 156.3, 132.8 (2 C), 129.0 (2 C), 128.9, 127.1, 79.1, 70.7, 55.2, 34.4, 28.2 (3 C), 25.9 and 10.6; *anti* isomer (distinct signals): δ_H 4.69 (1 H, d, J 9.3, N*H*), 2.73 (1 H, d, J 3.0, O*H*) and 0.93 (3 H, t, J 7.1, CH_2); δ_C 72.9, 56.2, 34.8, 22.6 and 10.4.

***tert*-Butyl (1*S*,2*S*)-1-benzyl-2-hydroxy-3-(phenylseleno)propylcarbamate (10c).** (1.5 g, 98%). Pale yellow solid, mp 139–141 °C; $[a]_D^{20}$ −11.8 (c 1.96 in $CHCl_3$); found: C, 59.8; H, 6.95; N, 3.0. Calc. for $C_{21}H_{27}NO_3Se$: C, 60.0; H, 6.5; N, 3.3%; δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.63–7.50 (2 H, m, Ar*H*), 7.36–7.12 (8 H, m, Ar*H*), 4.62 (1 H, d, J 7.8, N*H*), 4.04–3.68 (2 H, m, C*H*O and C*H*N), 3.30–3.12 (1 H, m, CH_2SeAr), 3.10 (1 H, br s, O*H*), 3.09–2.75 (3 H, m, CH_2SeAr and CH_2Ar) and 1.35 (9 H, s, 3 × CH_3); δ_C(50.3 MHz, $CDCl_3$) 155.8, 137.8, 134.2, 133.1 (2 C), 129.4, 129.3, 128.4 (2 C), 127.4, 126.4 (2 C), 123.5, 79.7, 72.2, 55.7, 35.8, 33.5 and 28.2 (3 C).

Preparation of *O*-protected γ-[*N*-(phenylseleno)alkyl]-2-nitrobenzenesulfonamides 4a–c. General procedure

A solution of β-hydroxyalkyl phenyl selenide **10c** (1.50 g, 3.56 mmol) in 12 : 1 dioxane–H_2SO_4 (26 mL) was stirred at room temperature for 1 h. The reaction was then quenched by careful addition of powdered sodium hydroxide (5.80 g, 145 mmol) and 8 mL of H_2O. The reaction mixture was then extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried over sodium sulfate and then evaporated. The crude residue was dissolved in dry CH_2Cl_2 (30 mL) at 0 °C. To this solution were added triethyl amine (0.69 mL, 4.98 mmol) and 2-nitrobenzenesulfonyl chloride (1.10 g, 4.98 mmol). The mixture was warmed to room temperature and stirred for 14 h. A 7% solution of hydrochloric acid (50 mL) and CH_2Cl_2 (30 mL) was then added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated

in vacuo. The crude residue was dissolved in dry Et_2O (30 mL) and 3,4-dihydro-2*H*-pyran (0.40 mL, 4.2 mmol) was added. *p*-Toluenesulfonic acid monohydrate (190 mg, 1 mmol) was added to this solution which was then stirred at room temperature for 21 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (Et_2O 40% in light petroleum) to give **4c**. By the same procedure **4a** and **4b** were prepared. Yields, as well as physical and spectral data are reported below.

***N*-{(1*S*,2*R*) and (1*S*,2*S*) 1-(Cyclohexylmethyl)-3-(phenylseleno)-2-[(2*R**)-tetrahydro-2*H*-pyran-2-yloxy]propyl}-2-nitrobenzenesulfonamide (4a).** (1.4 g, 74%). Colourless oil (found: C, 54.9; H, 5.7; N, 5.1. Calc. for $C_{27}H_{36}N_2O_6SSe$: C, 54.45; H, 6.1; N, 4.7%); 4 : 1 mixture of four stereoisomers. Only the signals of the *syn* isomer are indicated below. *syn* Isomer: 1 : 1 mixture of two diastereoisomers. δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.30–8.20 (2 H, m, Ar*H*), 7.95–7.80 (4 H, m, Ar*H*), 7.78–7.63 (2 H, m, Ar*H*), 7.50–7.32 (4 H, m, Ar*H*), 7.30–7.15 (6 H, m, Ar*H*), 5.67 (1 H, d, *J* 9.2, N*H*), 5.61 (1 H, d, *J* 8.8, N*H*), 4.62–4.48 (2 H, m, 2 × OC*H*O), 4.21–3.67 (4 H, m, 2 × C*H*O and 2 × C*H*N), 3.62–3.28 (4 H, m, 2 × CH_2O), 3.07–2.64 (4 H, m, 2 × CH_2SeAr) and 1.95–0.60 (38 H, m, 2 × CH and 18 × CH_2); δ_C(50.3 MHz, $CDCl_3$) 147.4 (2 C), 136.6 (2 C), 135.0, 134.8, 133.3, 132.9, 132.7, 132.4, 132.2, 132.1, 131.4 (2 C), 130.3, 130.2, 129.5 (2 C), 129.0 (2 C), 126.9, 126.6, 125.1, 125.0, 101.1, 97.5, 79.9, 75.7, 63.0, 62.9, 53.9, 53.1, 40.8, 39.9, 33.7, 33.5, 33.1, 33.0, 32.9, 32.8, 31.0, 30.7, 27.9, 27.7, 26.1, 25.8 (2 C), 25.3, 25.2, 25.0, 19.6, 19.5 and 19.4 (2 C).

***N*-{(1*S*,2*R*) and (1*S*,2*S*) 1-Ethyl-3-(phenylseleno)-2-[(2*R**)-tetrahydro-2*H*-pyran-2yloxy]propyl}-2-nitrobenzenesulfonamide (4b).** (1.6 g, 86%). Colourless oil (found: C, 50.3; H, 5.2; N, 5.0. Calc. for $C_{22}H_{28}N_2O_6SSe$: C, 50.1; H, 5.35; N, 5.3%); 4 : 1 mixture of four stereoisomers. Only the signals of the *syn* isomer are indicated below. *syn* Isomer: 1 : 1 mixture of two diastereoisomers. δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.22–8.10 (2 H, m, Ar*H*), 7.88–7.76 (2 H, m, Ar*H*), 7.74–7.61 (4 H, m, Ar*H*), 7.50–7.32 (4 H, m, Ar*H*), 7.28–7.15 (6 H, m, Ar*H*), 5.78 (1 H, d, *J* 8.2, N*H*), 5.75 (1 H, d, J 9.1, N*H*), 4.60–4.50 (2 H, m, 2 × OC*H*O), 3.99–3.56 (6 H, m, 2 × C*H*O, 2 × C*H*N and CH_2O), 3.52–3.35 (2 H, m, CH_2O), 3.31 (1 H, dd, *J* 12.8 and 3.7, CH_2SeAr), 2.97 (1 H, dd, *J* 12.8 and 5.3, CH_2SeAr), 2.73 (1 H, dd, *J* 12.7 and 8.0, CH_2SeAr), 2.62 (1 H, dd, *J* 12.7 and 10.1, CH_2SeAr), 1.89–1.32 (16 H, m, 8 × CH_2), 0.81 (3 H, t, *J* 7.5, CH_2CH_3) and 0.80 (3 H, t, *J* 7.3, CH_2CH_3); δ_C(50.3 MHz, $CDCl_3$) 151.2, 150.1, 135.5, 135.3, 133.2, 133.1, 132.9, 132.8 (2 C), 132.4, 132.3, 131.4, 130.4, 130.3, 129.7, 129.6, 129.2 (2 C), 129.1, 127.1, 126.7, 125.1(2 C), 124.8, 101.4, 97.7, 79.1, 75.2, 63.6, 63.0, 58.4, 57.5, 30.8, 30.7, 28.0 (2 C), 26.8, 26.1, 25.1(2 C), 20.0, 19.6, 10.6 and 10.3.

***N*-{(1*S*,2*S*)-1-Benzyl-3-(phenylseleno)-2-[(2*R**)-tetrahydro-2*H*-pyran-2-yloxy]-propyl}-2-nitrobenzenesulfonamide (4c).** (1.5 g, 71%). Pale yellow oil (found: C, 55.3; H, 4.6; N, 4.5. Calc. for $C_{27}H_{30}N_2O_6SSe$: C, 55.0; H, 5.1; N, 4.75%); mixture of diastereoisomers (95 : 5). *Major* isomer: δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.75–7.64 (2 H, m, Ar*H*), 7.60–7.12 (8 H, m, Ar*H*), 7.02–6.82 (4 H, m, Ar*H*), 4.63–4.44 (1 H, m, OC*H*O), 4.30–3.40 (5 H, m, N*H*, C*H*O, C*H*N and CH_2O), 3.13 (1 H, dd, *J* 12.70 and 8.3, CH_2SeAr), 2.96 (1 H, dd, *J* 12.7 and 5.7, CH_2SeAr), 2.89 (1 H, dd, *J* 14.0 and 4.4, CH_2Ar), 2.72 (1 H, dd, *J* 14.0 and 10.0, CH_2Ar) and 1.95–1.46 (6 H, m, 3 × CH_2); δ_C(50.3 MHz, $CDCl_3$) 146.6, 137.5, 135.1, 132.5, 132.4 (2 C), 132.1, 130.0, 129.6, 129.2 (2 C), 129.1, 129.0, 128.8, 127.7, 126.7, 126.1, 124.5, 102.3, 84.7, 65.1, 59.5, 35.2, 30.9, 30.4, 24.5, and 21.3.

Typical procedure for the conversion of γ-[*N*-(phenylseleno)alkyl]-arylsulfonamides into *N*-aryl-azetidines

Commercial *m*-chloroperoxybenzoic acid (0.40 g, 2.36 mmol) was added to a mixture of **4c** (0.35 g, 0.59 mmol) and powdered potassium hydrogenphosphate (0.51 g, 2.95 mmol) in tetrahydrofuran (15 mL) at room temperature. The resulting mixture was stirred and the progress of the reaction was monitored by TLC. When the selenide was completely consumed (3 h) powdered potassium hydroxide (0.24 g, 4.42 mmol) was added and stirring was continued until the selenone was consumed (6 h). The mixture was then diluted with water (30 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over sodium sulfate and evaporated. The crude product was dissolved in MeOH (20 mL) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol) was added. This solution was then stirred at room temperature for 16 h. This final deprotection treatment was effected only to obtain products **11a–c**. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using a mixture of Et_2O–light petroleum (70 : 30) as eluant to give **11c**. Yields, physical and spectral data of the new compounds are reported below.

(2*S*,3*S)-2-(Cyclohexylmethyl)-1-[(2nitrophenyl)sulfonyl] azetidine-3-ol (11a).** (0.26 g, 61%). Colourless oil (found: C, 54.5; H, 6.6; N, 7.6. Calc. for $C_{16}H_{22}N_2O_5S$: C, 54.2; H, 6.25; N, 7.9%); ν_{max}/cm^{-1} 3528, 2923, 1558, 1371 and 1167; 82 : 18 mixture of two diastereoisomers. *Major* isomer: δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.06–7.92 (1 H, m, Ar*H*), 7.80–7.60 (3 H, m, ArH), 4.65–4.45 (1 H, m, C*H*O), 4.33 (1 H, dd, *J* 9.5 and 6.5, CH_2N), 3.73 (1 H, dd, *J* 9.5 and 2.8, CH_2N), 3.45–3.33 (1 H, m, C*H*N), 2.22 (1 H, s, O*H*) and 1.85–0.75 (13 H, m, C*H* and CH_2); δ_C(50.3 MHz, $CDCl_3$) 148.3, 133.8, 131.8, 131.6, 130.6, 124.1, 68.4, 63.4, 58.8, 35.6, 34.2, 33.2, 33.0 and 25.6 (3 C); *minor* isomer (distinct signals): δ_C(50.3 MHz, $CDCl_3$) 133.3, 132.9, 130.8, 125.2, 73.2, 66.7, 58.2, 33.9 and 32.6; *m*/*z* (E/I) 311 (47, M − 43), 215 (20%), 186 (100), 109 (18), 83 (19) and 55 (11).

(2*S*,3*S)-3-Ethyl-1-[(2-nitrophenyl)sulfonyl]azetidine-3-ol (11b).** (0.2 g, 56%). White solid, mp 118–121 °C (found: C, 46.0; H, 5.35; N, 9.5. Calc. for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.9; N, 9.8%); ν_{max}/cm^{-1} 3431, 2963, 1547, 1352 and 1164; 83 : 17 mixture of diastereoisomers. *Major* isomer: δ_H(200 MHz, CD_3OD, Me_4Si) 8.08–7.97 (1 H, m, Ar*H*), 7.88–7.79 (3 H, m, Ar*H*), 4.38 (1 H, dd, *J* 6.8 and 3.3, C*H*O), 4.34–4.22 (1 H, m, C*H*N), 4.24 (1 H, dd, *J* 9.2 and 6.8, CH_2N), 3.73 (1 H, dd, *J* 9.2 and 3.3, CH_2N), 2.09–1.64 (2 H, m, CH_2CH$_3$) and 0.90 (3 H, t, *J* 7.5, CH_2CH_3); δ_C(50.3 MHz, CD_3OD) 149.6, 135.0, 132.6, 131.5, 131.0, 125.0, 72.4, 62.9, 59.3, 22.5 and 9.8; *minor* isomer (distinct signals): δ_H(200 MHz, CD_3OD, Me_4Si) 4.16–3.97 (2 H, m, C*H*O and CH_2N), 3.70–3.62 (1 H, m, CH_2N) and 0.95 (3 H, t, *J* 7.5, CH_2CH_3); δ_C(50.3 MHz, CD_3OD) 148.2, 131.7, 76.4, 65.6, 58.8, 26.9 and 8.5.

(2*S*,3*R*)-2-Benzyl-1-[(2-nitrophenyl)sulfonyl]azetidin-3-ol (11c). (0.1 g, 50%). Pale yellow oil (found: C, 54.8; H, 4.9; N, 7.6. Calc. for $C_{16}H_{16}N_2O_5S$: C, 55.2; H, 4.6; N, 8.0%); $[\alpha]_D^{27}$ 118.5 (*c* 1.31 in $CHCl_3$); ν_{max}/cm^{-1} 3470, 2894, 1540, 1349 and 1162; δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.95–7.85 (1 H, m, Ar*H*), 7.78–7.61 (3 H, m, Ar*H*), 7.35–7.17 (5 H, m, Ar*H*), 4.42 (1 H, dt, *J* 8.8 and 5.2, C*H*N), 4.24 (1 H, dt, *J* 6.7 and 5.2, C*H*O), 4.06 (1 H, dd, *J* 8.1 and 6.7, CH_2N), 3.72 (1 H, dd, *J* 8.1 and 5.2, CH_2N), 3.21 (1 H, dd, *J* 13.8 and 5.2, CH_2Ar), 2.96 (1 H, dd, *J* 13.8 and 8.8, CH_2Ar) and 2.05 (1 H, br s, OH); δ_C(50.3 MHz, $CDCl_3$) 148.6, 135.6, 134.1, 131.8, 130.9, 129.7, 129.4 (2 C), 128.5 (2 C), 126.7, 124.1, 74.1, 65.1, 58.0 and 39.3.

Methyl (*S*)-2-{[(4-methylphenyl)sulfonyl]amino}-4-(phenylseleno)butanoate (4d). Compound **13** was prepared in 78% yield by standard acylation procedure[32] from commercially available (*S*)-(−)-α-amino-γ-butyrolactone hydrobromide **12**. Ester **4d** was synthesized by cleavage of the corresponding lactone **13** with sodium phenyl selenolate in refluxing DMF[22] followed by treatment of the crude acid with an ethereal solution of diazomethane. Purification by column chromatography on silica gel using a mixture of Et_2O–light petroleum (60 : 40) as eluant gave **4d** (2.8 g, 83%) as a pale yellow solid, mp 66–67 °C; $[\alpha]_D^{26}$ 4.1 (*c* 1.65 in $CHCl_3$); (found: C, 50.5; H, 5.2; N, 3.0. Calc. for $C_{18}H_{21}NO_4SSe$: C, 50.7; H, 4.9; N, 3.3%); δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.76–7.67 (2 H, m, Ar*H*), 7.48–7.36 (2 H, m, Ar*H*), 7.34–7.21 (5 H, m, Ar*H*), 5.31 (1 H, d, *J* 9.0, N*H*), 4.06 (1 H, ddd, *J* 9.0, 8.3 and 4.8, C*H*N), 3.49 (3 H, s, OCH_3), 3.01–2.73 (2 H, m, ArSeCH_2), 2.42 (3 H, s, CH_3) and 2.17–1.84 (2 H, m, CH_2); δ_C(50.3 MHz, $CDCl_3$) 171.5, 143.6, 136.3, 132.7 (2 C), 129.5 (2 C), 129.0, 128.9 (2 C), 127.1 (2 C), 127.0, 55.3, 52.4, 33.5, 22.7 and 21.4; *m*/*z* (E/I) 427 (M^+, 11%), 272 (29), 210 (13), 185 (14), 157 (33), 155 (60), 114 (73), 91 (100), 65 (15) and 56 (24).

The oxidation–cyclization reaction of **4d** was effected as reported above for **4a–c**. After purification by column chromatography on silica gel (CH_2Cl_2 as eluant), the azetidine ester (***S*)-6d** (0.1 g, 44%) was obtained.

***N*-[(1*S*)-1-(Hydroxymethyl)-3-(phenylseleno)propyl]-4-methylbenzenesulfonamide (14).** To a solution of the ester **4d** (1.30 g, 3.04 mmol) in THF (30 mL), lithium aluminium hydride (6.7 mL, 1.0 M in THF, 6.70 mmol) was added dropwise at 0 °C. After 2 h the reaction was quenched by addition of water (5 mL). The mixture was partitioned between saturated aq. NH_4Cl (30 mL) and Et_2O (40 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient: 3–20% MeOH in CH_2Cl_2) to give **14** (0.9 g, 73%) as a white solid, mp 92 °C; $[\alpha]_D^{27}$ −1.15 (*c* 1.50 in $CHCl_3$); (found: C, 51.0; H, 5.5; N, 3.2. Calc. for $C_{17}H_{21}NO_3SSe$: C, 51.25; H, 5.3; N, 3.5%); ν_{max}/cm^{-1} 3318, 2935, 1435, 1322 and 1155; δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.82–7.70 (2 H, m, Ar*H*), 7.40–7.27 (7 H, m, Ar*H*), 5.39 (1 H, d, *J* 8.0, N*H*), 3.63–3.32 (3 H, m, C*H*N and CH_2OH), 2.85–2.53 (2 H, m, ArSeCH_2) 2.48 (1 H, br s, O*H*) 2.40 (3 H, s, CH_3) and 1.85–1.70 (2 H, m, CH_2); δ_C(50.3 MHz, $CDCl_3$) 143.6, 137.5, 132.5 (2 C), 129.8 (2 C), 129.6, 129.0 (2 C), 127.0 (2 C), 126.9, 64.5, 55.2, 31.9, 23.5 and 21.5; *m*/*z* (E/I): 399 (M^+, 18%) 242 (13), 197 (47), 171 (19), 155 (61), 91 (100), 77 (12) and 56 (29).

4-Methyl-*N*-((1*S*)-3-(phenylseleno)-1-{[(2*S)-tetrahydro-2*H*-pyran-2-yloxy]methyl}propyl)benzenesulfonamide (4e).** The alcohol **14** (0.30 g, 0.75 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and 3,4-dihydro-2*H*-pyran (0.14 mL, 1.50 mmol) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) were added. The resulting mixture was stirred at room temperature for 18 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of Et_2O–light petroleum (40 : 60) as eluant to give **4e** (0.3 g, 80%) as a colourless oil (found: C, 54.55; H, 6.3; N, 2.7. Calc. for $C_{22}H_{29}NO_4SSe$: C, 54.8; H, 6.1; N, 2.9%); 1 : 1 mixture of two diastereoisomers. δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.80–7.69 (4 H, m, Ar*H*), 7.48–7.37 (4 H, m, Ar*H*), 7.32–7.14 (10 H, m, Ar*H*), 5.58 (1 H, d, *J* 8.0, N*H*), 5.20 (1 H, d, *J* 8.1, N*H*), 4.92–4.84 (1 H, m, OC*H*O), 4.61–4.50 (1 H, m, OC*H*O), 4.36–4.25 (2 H, m, C*H*N), 4.08–3.60 (3 H, m, 2 × CH_2O), 3.59–3.29 (5 H, m, 2 × CH_2O), 3.22–3.10 (1 H, m, ArSeCH_2), 3.01–2.72 (3 H, m, 2 × ArSeCH_2) 2.40 (6 H, s, CH_3), 1.99–1.28 (12 H, m, 6 × CH_2) and 0.94–0.76 (4 H, m, 2 × CH_2); δ_C(50.3 MHz, $CDCl_3$) 143.2, 143.1, 138.0, 137.9, 132.5 (2 C), 132.4 (2 C), 129.5 (6 C), 128.9 (4 C), 127.0 (4 C), 126.8, 126.7, 100.0, 99.0, 70.2, 68.5, 63.1, 62.4, 53.4, 53.3, 33.0 (2 C), 30.4, 30.3, 25.1, 25.0, 23.7, 23.6, 21.4 (2 C), 19.8 and 19.3.

The oxidation–cyclization reaction of **4e** was effected as reported for **4a–c** and afforded, after purification by column chromatography on silica gel (gradient: 80–100% Et_2O in light petroleum), the optically active azetidine alcohol (***S*)-6e** (0.1 g, 62%).

3-Benzyldihydrofuran-2(3*H*)-one (16). To a round-bottom flask equipped with a dropping funnel, diisopropylamine (0.57 mL, 4.40 mmol) in 30 mL of THF was added at −78 °C and the solution was treated with the equivalent amount of *n*-butyllithium (2.75 mL, 1.6 M in hexane, 4.40 mmol). To this solution the γ-butyrolactone **15** (0.31 mL, 4.0 mmol) was added followed by addition of benzyl bromide (0.57 mL, 4.80 mmol) in 5 ml of THF after 20 minutes. Stirring was continued at −78 °C for 1 h and the reaction was then quenched with saturated aq. NH_4Cl solution, extracted with Et_2O (2 × 30 mL), dried over sodium sulfate, filtered and evaporated. Purification by column chromatography on silica gel (gradient: 50–70% Et_2O in light petroleum) gave the α-benzyl lactone **16** (0.5 g, 70%) as a pale yellow oil; *m*/*z* (E/I): 176 (M^+, 85%), 147 (100), 104 (44), 91 (99), 77 (12) and 65 (21).

(2*R*)-2-Benzyl-4-(phenylseleno)butanoic acid (17)

The lithium enolate of **22** (generated with LDA in THF at −78 °C) was protonated with a chiral proton source (*R*-pantolactone) as reported in the literature[26] to give (***R*)-16** in 92% yield; $[\alpha]_D^{22}$ −12.6 (*c* 2.42 in $CHCl_3$); HPLC analysis (Chiracel OD-H column, 250 × 4.6 mm, Daicel, 4% 2-propanol in hexane, flow rate 1 mL min^{-1}, UV detection at 220 nm) showed an er of 61 : 39 (t_r: 27.1 min for the minor enantiomer; t_r: 28.5 min for the major enantiomer). The γ-lactone (***R*)-16** (0.64 g, 3.64 mmol) by treatment with sodium phenyl selenolate in refluxing DMF[22] for 5 h and after quenching by careful addition of hydrochloric acid (20% in water, 20 mL)

gave the corresponding acid **17**. The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using a mixture of Et_2O–light petroleum (50 : 50) as eluant to give the acid **17** (1.2 g, 75%) as a pale yellow oil (found: C, 61.0; H 5.8. Calc. for $C_{17}H_{18}O_2Se$: C 61.3; H 5.4%); ν_{max}/cm^{-1} 3026, 1704, 1437 and 1235; δ_H(200 MHz, $CDCl_3$, Me_4Si) 9.92 (1 H, br s, COO*H*), 7.48–7.07 (10 H, m, Ar*H*), 3.10–2.68 (5 H, m, CH_2 and C*H*) and 2.19–1.75 (2 H, m, CH_2); δ_C(50.3 MHz, $CDCl_3$) 181.1, 138.3, 132.6, 129.4, 128.9 (3 C), 128.7 (2 C), 128.3 (2 C), 126.8, 126.4, 46.9, 37.5, 31.4 and 24.9.

***N*-[(1*R*)-1-Benzyl-3-(phenylseleno)propyl]-2-nitrobenzenesulfonamide (4f).** Acid **17** (0.92 g, 2.75 mmol) was reacted with oxalyl chloride (0.40 mL, 4.12 mmol) at room temperature for 5 h. The solution was evaporated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (5 mL), the solvent was removed and the residue immediately dissolved in dry CH_2Cl_2 (4 mL) and used for the next reaction. Freshly distilled $TMSN_3$ (1.42 mL, 3.30 mmol) was added to this solution and the mixture was refluxed for 5 h and then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in THF (6 mL). To the stirred solution of the isocyanate, 1 N NaOH (3 mL) was added dropwise. The mixture was heated at reflux for 4 h. After addition of Et_2O (20 mL), the two phases were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded the crude amine **18** which was acylated in the next step. The amine **18** (0.64 g, 2.1 mmol) was dissolved in dry CH_2Cl_2 (20 mL) at 0 °C. To this solution triethyl amine (0.36 mL, 2.6 mmol) and 2-nitrobenzenesulfonyl chloride (0.58 g, 2.6 mmol) were added. The mixture was warmed to room temperature and stirred for 5 h before being partitioned between saturated aq. NH_4Cl (30 mL) and CH_2Cl_2 (30 mL). The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using a mixture of EtOAc–light petroleum (20 : 80) as eluant to give the γ-[*N*-(phenylseleno)alkyl]arylsulfonamide **4f** (0.7 g, 55%), colourless oil (found: C, 53.6; H; 4.8; N, 5.5. Calc. for $C_{22}H_{22}N_2O_4SSe$: C, 53.9; H, 4.5; N, 5.7%); $[\alpha]_D^{25}$ −2.3 (*c* 1.25 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.02–7.92 (1 H, m, Ar*H*), 7.80–7.70 (1 H, m, Ar*H*), 7.68–7.58 (2 H, m, Ar*H*), 7.47–7.33 (2 H, m, Ar*H*), 7.33–7.18 (3 H, m, Ar*H*), 7.13–6.82 (5 H, m, Ar*H*), 5.41 (1 H, d, *J* 8.2, N*H*), 4.04–3.83 (1 H, m, C*H*N), 3.09–2.65 (4 H, m, ArCH_2 and ArSeCH_2) and 2.01–1.86 (2 H, m, CH_2); δ_C(50.3 MHz, $CDCl_3$) 136.6, 134.5, 133.0, 132.9, 132.8 (2 C), 130.2, 129.2, 129.1 (3 C), 129.0 (2 C), 128.2 (2 C), 126.9, 126.7, 125.3, 55.8, 41.6, 35.6 and 23.6.

(2*R*)-2-Benzyl-1-[(2-nitrophenyl)sulfonyl]azetidine (6f). The oxidation–cyclization reaction of **4f** was carried out as reported above for compound **4d** and gave, after purification by column chromatography on silica gel using a mixture of Et_2O–light petroleum (50 : 50) as eluant, the optically active azetidine (***R*)-6f** (0.2 g, 80%) as a white solid, mp 100 °C (found: C, 57.6; H, 5.0; N, 8.3. Calc. for $C_{16}H_{16}N_2O_4S$: C, 57.8; H, 4.85; N, 8.4%); $[\alpha]_D^{22}$ −34.2 (*c* 2.46 in $CHCl_3$); ν_{max}/cm^{-1} 2893, 1717, 1539, 1369 and 1162; HPLC analysis (Chiracel OD-H column, 250 × 4.6 mm, Daicel, 8% 2-propanol in hexane, flow rate 1 mL min^{-1}, UV detection at 230 nm) showed an er of 55 : 45; t_r: 30.6 min for the minor enantiomer; t_r: 41.1 min for the major enantiomer; δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.90–7.78 (1 H, m, Ar*H*), 7.70–7.53 (3 H, m, Ar*H*), 7.28–7.04 (5 H, m, Ar*H*), 4.60 (1 H, ddt, *J* 8.9, 4.7 and 8.1, C*H*N), 3.90 (1 H, dt, *J* 8.5 and 8.4, CH_2N), 3.81–3.69 (1 H, m, CH_2N), 3.11 (1 H, dd, *J* 13.6 and 4.7, ArCH_2), 2.88 (1 H, dd, *J* 13.6 and 8.9, ArCH_2) and 2.09–1.92 (2 H, m, CH_2); δ_C(50.3 MHz, $CDCl_3$) 148.6, 136.0, 133.7, 131.7, 130.7, 130.4, 129.2 (2 C), 128.3 (2 C), 126.5, 124.0, 64.9, 48.4, 41.9 and 21.4; *m*/*z* (E/I): 176 (56, M − 156), 147 (80), 131 (17), 117 (16), 104 (30), 91 (100) and 65 (15%).

(2*S*)-4-(Phenylseleno)butan-2-ol (20). To a stirred solution of ethyl (*S*)-3-hydroxybutyrate **19** (1 mL, 7.65 mmol) and 3,4-dihydro-2*H*-pyran (0.84 mL, 9.20 mmol) in Et_2O (70 mL), $TsOH{\cdot}H_2O$ (190 mg, 1 mmol) was added in one portion at room temperature. After 48 h the mixture was chilled to 0 °C and lithium aluminium hydride (16.5 mL, 1.0 M in THF, 16.50 mmol) was added dropwise. After 5 h the reaction was quenched by careful addition of water (10 mL). The mixture was partitioned between saturated aq. NH_4Cl (30 mL) and Et_2O (40 mL), and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 40 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was dissolved in THF (50 mL). Phenyl selenocyanate (1.09 mL, 8.96 mmol) and tributylphosphine (2.2 mL, 8.96 mmol) were added at room temperature. The resulting mixture was stirred and the progress of the reaction was monitored by TLC. When the alcohol was completely consumed (8 h) the reaction mixture was concentrated *in vacuo*. The residue was then diluted with MeOH (50 mL) and *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol) was added to the solution, which was then stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel (gradient: 40–60% Et_2O in light petroleum) gave the optically pure γ-hydroxyselenide **20**[34] (1.2 g, 71%) as a colourless oil; $[\alpha]_D^{22}$ 40.6 (*c* 2.19 in $CHCl_3$).

***N*-[(1*R*)-1-Methyl-3-(phenylseleno)propyl]-2-nitrobenzenesulfonamide (4g).** To a stirred solution of the alcohol **20** (1.80 g, 7.83 mmol) and phthalimide (1.61, 10.90 mmol) in THF (30 mL), triphenylphosphine (2.80 g, 10.9 mmol) was added. DIAD (1.96 mL, 10.10 mmol) was subsequently added dropwise at 0 °C. After 7 h the reaction mixture was concentrated *in vacuo*, the residue dissolved in a mixture of Et_2O–light petroleum (50 : 50) and passed through a silica gel pad. The filtrate was concentrated and the crude phthalimide derivative was employed in the following step. The phthalimide was dissolved in ethanol (100 mL) and immediately treated with hydrazine hydrate (0.5 mL, 10.14 mmol). After stirring for 2 h at 110 °C, the reaction mixture was allowed to slowly reach room temperature and concentrated. After the addition of CH_2Cl_2 (50 mL) the suspension was filtered. The filtrate was dried over sodium sulfate and evaporated. The crude amine was dissolved in dry CH_2Cl_2 (80 mL) at 0 °C. To this solution triethyl amine (1.41 mL, 10.91 mmol) and 2-nitrobenzenesulfonyl chloride (2.408 g, 10.91 mmol) were added. The mixture was warmed to room temperature and stirred for 15 h before being partitioned between aq. HCl (7%, 30 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted

with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluant and **4g** (2.3 g, 71%) was obtained as a pale yellow solid, mp 87–89 °C (found: C, 46.7; H, 4.6; N, 6.4. Calc. for $C_{16}H_{18}N_2O_4SSe$: C, 46.5; H, 4.4; N 6.8%); $[\alpha]_D^{22}$ −45.3 (*c* 1.83 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.18–8.10 (1 H, m, Ar*H*), 7.86–7.79 (1 H, m, Ar*H*), 7.75–7.65 (2 H, m, Ar*H*), 7.45–7.35 (2 H, m, ArH), 7.31–7.19 (3 H, m, Ar*H*), 5.18 (1 H, d, *J* 7.3, N*H*), 3.74–3.63 (1 H, m, C*H*N), 2.92 (1 H, ddd, *J* 12.4, 8.2 and 6.0, ArSeCH_2), 2.82 (1 H, ddd, *J* 12.4, 8.3 and 7.2, ArSeCH_2), 1.90–1.72 (2 H, m, CH_2) and 1.09 (3 H, t, *J* 5.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 147.6, 134.5, 133.4, 132.9. 132.5 (2 C), 130.6, 129.5, 129.0 (2 C), 126.9, 125.2, 50.9, 37.4, 23.1 and 21.5.

(2*R*)-2-Methyl-1-[(2-nitrophenyl)sulfonyl]azetidine (6g). The oxidation–cyclization reaction of **4g** was effected as reported above for **4d** and gave, after purification by column chromatography on silica gel using a mixture of Et_2O–light petroleum (40 : 60) as eluant, the enantiomerically pure azetidine **6g** (0.2 g, 59%) as a white solid, mp 42 °C (found: C, 46.5; H, 5.0; N, 10.6. Calc. for $C_{10}H_{12}N_2O_4S$: C, 46.9; H, 4.7; N, 10.9%); $[\alpha]_D^{21}$ −115.2 (*c* 1.09 in $CHCl_3$); ν_{max}/cm^{-1} 3090, 2980, 1541, 1333 and 1158; HPLC analysis (*R*,*R*-Whelk O1 column, 250 × 4.6 mm, Merck KGaA, 4% 2-propanol in hexane, flow rate 2 mL min^{-1}, UV detection at 250 nm) showed an er > 99 : 1; t_r: 18.7 min; δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.05–7.92 (1 H, m, Ar*H*), 7.77–7.61 (3 H, m, ArH), 4.53 (1 H, tq, *J* 8.2 and 6.3, C*H*N), 3.98 (1 H, dt, *J* 9.1 and 7.9, CH_2N), 3.85 (1 H, ddd, *J* 9.1, 7.9 and 3.8, CH_2N), 2.22 (1 H, dddd, *J* 10.8, 8.2, 7.9 and 3.8, CH_2), 1.96 (1 H, ddt, *J* 10.8, 8.2 and 7.9, CH_2), and 1.42 (3 H, d, *J* 6.3, CH_3); δ_C(50.3 MHz, $CDCl_3$) 148.7, 133.7, 131.6, 131.1, 130.7, 124.0, 61.4, 48.4, 23.7 and 22.1; *m*/*z* (E/I): 241 (9, M − CH_3), 239 (17%), 186 (100), 107 (6), 92 (6) and 56 (19).

1-(Phenylseleno)hexan-3-ol (23)

1-(Phenylseleno)hexan-3-one **22** was prepared as reported in the literature.[30] The asymmetric reduction of **22** was carried out under the conditions employed by Itsuno and Ito.[31] The crude alcohol was purified by column chromatography on silica gel using a mixture of Et_2O–light petroleum (30 : 70) as eluant and the optically active β-hydroxyselenide **23** (0.4 g, 87%) was obtained as a colourless oil (found: C, 55.9; H, 7.3. Calc. for $C_{12}H_{18}OSe$: C, 56.0; H, 7.05%); $[\alpha]_D^{21}$ −1.8 (*c* 1.24 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.58–7.40 (2 H, m, Ar*H*), 7.35–7.13 (3 H, m, Ar*H*), 3.82–3.60 (1 H, m, C*H*O), 3.12–2.89 (2 H, m, CH_2), 1.90–1.72 (2 H, m, CH_2), 1.65 (1 H, br s, O*H*), 1.55–1.16 (4 H, m, CH_2) and 0.91 (3 H, t, *J* 6.9, CH_3); δ_C(50.3 MHz, $CDCl_3$) 132.2 (2 C), 130.1, 128.9 (2 C), 126.5, 70.9, 39.3, 37.2, 23.9, 18.6 and 13.9; *m*/*z* (E/I): 258 (M^+, 100%), 185 (21), 171 (15), 157 (54), 100 (24), 72 (74) and 55 (54).

2-Nitro-*N*-{1-[2-(phenylseleno)ethyl]butyl} benzenesulfonamide (4h). Using the procedure described above for compound **20** the hydroxyselenide **23** was transformed into the γ-[*N*-(phenylseleno)alkyl]arylsulfonamide **4h** (1.4 g, 66%) which was obtained as a pale yellow solid, mp 75–77 °C (found: C, 48.65; H, 5.4; N, 6.1. Calc. for $C_{18}H_{22}N_2O_4SSe$: C, 48.9; H, 5.0; N, 6.35%); $[\alpha]_D^{21}$ 2.0 (*c* 1.02 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.20–8.18 (1 H, m, Ar*H*), 7.90–7.78 (1 H, m, Ar*H*), 7.76–7.64 (2 H, m, Ar*H*), 7.47–7.36 (2 H, m, Ar*H*), 7.32–7.20 (3 H, m, Ar*H*), 5.17 (1 H, d, *J* 8.6, N*H*), 3.75–3.55 (1 H, m, C*H*N), 2.99–2.71 (2 H, m, CH_2), 1.90–1.72 (2 H, m, CH_2), 1.50–1.06 (4 H, m, CH_2) and 0.79 (3 H, t, *J* 7.1, CH_3); δ_C(50.3 MHz, $CDCl_3$) 147.3, 134.5, 133.4, 132.7, 132.2 (2 C), 130.3, 129.6 (2 C), 128.9, 126.7, 125.0, 54.8, 37.0, 35.4, 32.3, 18.3 and 13.5; *m*/*z* (E/I): 412 (71, M − CH_3CH_2), 256 (54%), 227 (86), 210 (78), 173 (10), 156 (90), 108 (36), 92 (100), 72 (30) and 56 (19).

1-[(2-Nitrophenyl)sulfonyl]-2-propylazetidine (6h). The oxidation–cyclization reaction of **4h** was effected as reported above for **4g** and gave, after purification by column chromatography on silica gel using a mixture of Et_2O–light petroleum (40 : 60) as eluant, the optically active azetidine **6h** (0.1 g, 70%) as a colourless oil (found: C, 50.3; H, 5.9; N, 9.7. Calc. for $C_{12}H_{16}N_2O_4S$: C, 50.7; H, 5.7; N, 9.85%); $[\alpha]_D^{21}$ 10.1 (*c* 0.88 in $CHCl_3$); ν_{max}/cm^{-1} 2961, 1723, 1546, 1341 and 1166; HPLC analysis (Chiracel OD-H column, 250 × 4.6 mm, Daicel, 1% 2-propanol in hexane, flow rate 1 mL min^{-1}, UV detection at 230 nm) showed an er of 56 : 44; t_r: 66.8 min for the minor enantiomer; t_r: 71.1 min for the major enantiomer; δ_H(200 MHz, $CDCl_3$, Me_4Si) 8.08–7.91 (1 H, m, Ar*H*), 7.78–7.55 (3 H, m, Ar*H*), 4.42 (1 H, ddt, *J* 8.2, 4.6 and 4.4, C*H*N), 3.99 (1 H, dt, *J* 8.8 and 8.4, CH_2N), 3.81 (1 H, ddd, *J* 8.8, 8.1 and 4.1, CH_2N), 2.25–1.50 (4 H, m, 2 × CH_2), 1.38–1.08 (2 H, m, CH_2) and 0.89 (3 H, t, *J* 7.3, CH_3); δ_C(50.3 MHz, $CDCl_3$) 148.5, 133.8, 131.7, 130.7, 130.6, 124.0, 64.9, 48.5, 37.8, 21.8, 17.3 and 13.7; *m*/*z* (E/I): 241 (81, M − $CH_3CH_2CH_2$), 186 (100%), 98 (18) and 77 (13).

Acknowledgements

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

Notes and references

1 N. H. Cromwell and B. Phillips, *Chem. Rev.*, 1979, **79**, 331; J. A. Moore and R. S. Ayers, in *Small Ring Heterocycles*, ed. A. Hassner, Wiley, New York, 1983, vol. 2, D. E. Davies and R. C. Storr, in *Comprehensive Heterocyclic Chemistry*, ed. W. Lwowski, Pergamon, Oxford, 1984, vol. 7, pp. 238–284.

2 T. Okutani, T. Kaneko and K. Masuda, *Chem. Pharm. Bull.*, 1974, **22**, 1490; J. Kobayashi, J. Cheng, M. Ishibashi, M. P. Wälchli, S. Yamamura and Y. Ohizumi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1135; J. Frigola, A. Torrens, J. A. Castrillo, J. Mas, D. Vañó, J. M. Berrocal, C. Calvet, L. Salgado, J. Redondo, S. García-Granda, E. Valentí and J. R. Quintana, *J. Med. Chem.*, 1994, **37**, 4195; A. W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon, D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz, A. H. Dickenson, R. D. Porsolt, M. Williams and S. P. Arneric, *Science*, 1998, **279**, 77; J. W. Daly, H. M. Garraffo, T. F. Spande, M. W. Decker, J. P. Sullivan and M. Williams, *Nat. Prod. Rep.*, 2000, **17**, 131.

3 F. Couty, G. Evano and D. Prim, *Mini–Rev. Org. Chem.*, 2004, **1**, 133, and references cited therein.

4 A. V. Rama Rao, M. K. Gurjar and V. Kaiwar, *Tetrahedron: Asymmetry*, 1992, **3**, 859; A. P. Kozikowski, W. Tückmantel, Y. Liao, H. Manev, S. Ikonomovic and J. T. Wroblewski, *J. Med. Chem.*, 1993, **36**, 2706; J. Hoshino, J. Hiraoka, Y. Hata, S. Sawada and Y. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1995, 693; W. A. J. Starmans, R. W. A. Walgers, L. Thijs, R. De Gelder, J. M. M. Smits and B. Zwanenburg, *Tetrahedron*, 1998, **54**, 991.

5 G. Guanti and R. Riva, *Tetrahedron: Asymmetry*, 1995, **6**, 2921; W. A. J. Starmans, R. G. Doppen, L. Thijs and B. Zwanenburg,

Tetrahedron: Asymmetry, 1998, **9**, 429; W. L. Wu, M. A. Caplen, M. S. Domalski, H. Zhang, A. Fawzi and D. A. Burnett, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3157.
6 A. Duréault, M. Portal, F. Carreaux and J. C. Depezay, *Tetrahedron*, 1993, **49**, 4201; A. Marinetti, P. Hubert and J. P. Genêt, *Eur. J. Org. Chem.*, 2000, 1815.
7 M. Poch, X. Verdauguer, A. Moyano, M. A. Pericàs and A. Riera, *Tetrahedron Lett.*, 1991, **32**, 6935; Y. Hamada, F. Matsuura and T. Shioiri, *Tetrahedron*, 1994, **50**, 265; J. Barluenga, F. Fernández-Mari, A. L. Viado, E. Aguillar and B. Olano, *J. Org. Chem.*, 1996, **61**, 5659; H. Takikawa, T. Maeda, M. Seki, H. Koshino and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1997, 97; S. Knapp and Y. Dong, *Tetrahedron Lett.*, 1997, **38**, 3813; D. G. Liu and G. Q. Lin, *Tetrahedron Lett.*, 1999, **40**, 337; E. Fernández-Megía, M. A. Montaos and F. J. Sardina, *J. Org. Chem.*, 2000, **65**, 6780; H. Ohno, H. Hamaguchi and T. Tanaka, *J. Org. Chem.*, 2001, **66**, 1867; A. Münch, B. Wendt and M. Christmann, *Synlett*, 2004, 2751.
8 I. Ojima, M. Zhao, T. Yamato and K. Nakahashi, *J. Org. Chem.*, 1991, **56**, 5263; B. Krämer, T. Franz, S. Picasso, P. Pruschek and V. Jäger, *Synlett*, 1997, 295; B. Alcaide, P. Almendros, C. Aragoncillo and N. R. Salgado, *J. Org. Chem.*, 1999, **64**, 9596.
9 M. Shiozaki, H. Maruyama and N. Ishida, *Heterocycles*, 1984, **22**, 1725; D. J. Blythin, M. J. Green, M. J. R. Lauzon and H Shue, *J. Org. Chem.*, 1994, **59**, 6098; C. Agami, F. Couty and G. Evano, *Tetrahedron: Asymmetry*, 2002, **13**, 297; A. Carlin-Sinclair, F. Couty and N. Rabasso, *Synlett*, 2003, 726; F. Couty, G. Evano, M. Vargas-Sanchez and G. Bouzas, *J. Org. Chem.*, 2005, **70**, 9028.
10 J. Barluenga, B. Baragaña and J. M. Concellón, *J. Org. Chem.*, 1997, **62**, 5974; J. M. Concellón, P. L. Bernad and J. A. Pérez-Andrés, *Tetrahedron Lett.*, 2000, **41**, 1231.
11 S. Sengupta and D. Das, *Synth. Commun.*, 1998, **28**, 403; J. Wang, Y. Hou and P. Wu, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2277; A. C. B. Burtoloso and C. R. D. Correia, *Tetrahedron Lett.*, 2004, **45**, 3355.
12 M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini and C. Santi, *Chem.–Eur. J.*, 2004, **10**, 1752.
13 M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli and D. Bartoli, *Gazz. Chim. Ital.*, 1987, **117**, 423.
14 A. Toshimitsu, C. Hirosawa, S. Tanimoto and S. Uemura, *Tetrahedron Lett.*, 1992, **33**, 4017.
15 B. E. Evans, K. E. Rittle, C. F. Homnick, J. P. Springer, J. Hirshfield and D. F. Veber, *J. Org. Chem.*, 1985, **50**, 4615.
16 J. R. Luly, J. F. Dellaria, J. J. Plattner and Y. N. Soderquist, *J. Org. Chem.*, 1987, **52**, 1487.
17 W. T. Ashton, C. L. Cantone, L. C. Meurer, R. L. Tolman, W. J. Greenlee, A. A. Patchett, R. J. Lynch, T. W. Schorn, J. F. Strouse and P. K. S. Sieg, *J. Med. Chem.*, 1992, **35**, 2103.
18 A. Albeck and R. Persky, *J. Org. Chem.*, 1994, **59**, 653.
19 Formation of selenones as reaction intermediates was clearly demonstrated[12] by ^{1}H and ^{13}C NMR spectroscopy of the crude reaction mixture obtained prior to the addition of KOH. In particular a characteristic signal for the methylene linked to a selenonyl group was observed[20].
20 M. Tiecco, L. Testaferri, M. Tingoli and D. Chianelli, *Tetrahedron*, 1986, **42**, 4897.
21 Removal of the nosyl group was indeed effected in the case of the intermediate **6c**. The crude product was dissolved in MeCN (5 mL) and K_2CO_3 (0.35 g, 2.58 mmol) and benzenethiol (0.35 g, 3.20 mmol) were added and the solution was stirred at 50 °C for 1 h. The mixture was diluted with NaOH solution (10%, 20 mL) and extracted with diethyl ether (20 mL). The solvent was removed and the residue was purified by column chromatography on silica gel using a mixture of MeOH–CH_2Cl_2 (5 : 95) as eluant to give the *N*-deprotected azetidine (0.08 g, 51% calculated from **4c**). (2*S*,3*R*)-2-Benzyl-3-[(2*R**)-tetrahydro-2*H*-pyran-2-yloxy]azetidine was obtained as a pale yellow oil (found: C, 72.3; H, 8.9; N, 6.1. Calc. for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.6; N, 5.7%); $[\alpha]_D^{18}$ −76.3 (*c* 2.88 in $CHCl_3$); mixture of diastereoisomers (95 : 5). *Major* isomer: δ_H(200 MHz, $CDCl_3$, Me_4Si) 7.28–7.02 (5 H, m, Ar*H*), 4.55–4.43 (1 H, m, OC*H*O), 4.20–4.03 (1 H, m, C*H*N), 3.98 (1 H, s, N*H*), 3.79–3.21 (5 H, m, C*H*O, CH_2N and CH_2O), 3.01–2.76 (2 H, m, CH_2Ar), and 1.80–1.28 (6 H, m, 3 × CH_2); δ_C(50.3 MHz, $CDCl_3$) 138.4, 129.3 (2 C), 129.0 (2 C), 126.1, 98.2, 74.5, 68.2, 62.1, 50.3, 40.8, 30.3, 25.4, and 19.6. *Minor* isomer (distinct signals): δ_C(50.3 MHz, $CDCl_3$) 137.8, 129.1 (2 C), 128.6 (2 C), 126.4, 98.6, 67.9, 62.9, 51.5, 41.4, 29.6, and 20.2. *m*/*z* (E/I) 218 (8, M − CH_3CH_2), 162 (29%), 134 (15), 120 (69), 91 (24), 85 (100) and 57 (14):T. W. Green and P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, Wiley, New York, 4th edn, 2007; P. J. Kocienski, in *Protecting Groups*, Thieme, Stuttgart, 3rd edn, 2004.
22 D. Liotta, U. Sunay, H. Santiesteban and W. Markiewicz, *J. Org. Chem.*, 1981, **46**, 2605.
23 T. Ibuka, K. Nakai, H. Habashita, Y. Hotta, A. Otaka, H. Tamamura and N. Fujii, *J. Org. Chem.*, 1995, **60**, 2044.
24 B. I. Ericksson, S. Carlsson, M. Halvarsson, B. Risberg and C. Mattsson, *Thromb. Haemostasis*, 1997, **78**, 1404; A. Zagari, G. Nemethy and H. A. Scheraga, *Biopolymers*, 1990, **30**, 967; T. J. Deming, M. J. Fournier, T. L. Mason and D. A. Tirrel, *Macromolecules*, 1996, **29**, 1442; G. Schlechtingen, R. N. Dehaven, J. D. Daubert, J. Cassel and M. Goodmann, *Biopolymers*, 2003, **71**, 71.
25 W. Behnen, C. Dauelsberg, S. Wallbaum and J. Martens, *Synth. Commun.*, 1992, **22**, 2143; M. Yamaguchi, T. Shiraishi and M. Hirama, *J. Org. Chem.*, 1996, **61**, 3520; W. A. J. Starmans, R. W. A. Walgers, L. Thijs, R. de Gelder, J. M. M. Smits and B. Zwaneburg, *Tetrahedron*, 1998, **54**, 4991.
26 U. Gerlach, T. Haubenreich, S. Hünig and N. Klaunzer, *Chem. Ber.*, 1994, **127**, 1989.
27 M. Khoukhi, M. Vaultier, A. Benalil and B. Carboni, *Synthesis*, 1996, 483.
28 H. Lebel and O. Leogane, *Org. Lett.*, 2005, **7**, 4107.
29 O. Mitsunobu, *Synthesis*, 1981, 1.
30 M. Miyashita and A. Yoshikoshi, *Synthesis*, 1980, 664.
31 S. Itsuno and K. Ito, *J. Org. Chem.*, 1984, **49**, 555.
32 S. Natelson and E. A. Natelson, *Microchem. J.*, 1989, **40**, 226.
33 T. Flechtner, *J. Org. Chem.*, 1977, **42**, 901.
34 K. Haraguchi, H. Tanaka and T. Miyasaka, *Synthesis*, 1989, 434.