# Stereocontrolled Synthesis of 1,2-Dialkyl-4-halopyrrolidines through PhSeX-Induced Cyclization of Secondary Homoallylamines

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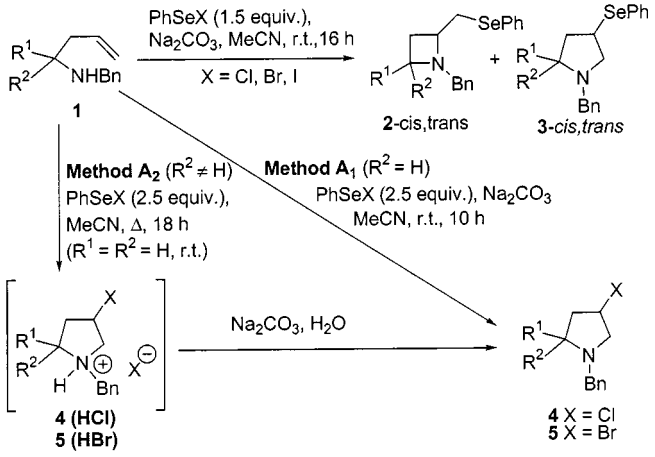
The selenium-induced cyclization of α-alkyl or α,α-dialkyl-homoallyl-benzylamines **1** by use of PhSeX (X = Cl, Br, I; 1.5 equiv.) provided a mixture of (phenylselanylmethyl)azetidines **2** and (phenylselanyl)pyrrolidines **3**.[1] When an excess of PhSeX (X = Cl, Br) was used, 4-halopyrrolidines **4** (X = Cl) or **5** (X = Br) were formed and isolated in very good yields. Mono- or dialkyl 4-halopyrrolidines **4** and **5** could also be obtained stereospecifically by $SO_2Cl_2$ or $Br_2$ treatment of 4-(phenylselanylmethyl)azetidines **2**, by way of the intermediate (halomethyl)azetidines **14** (X = Cl) or **15** (X = Br). When starting from 4-(phenylselanyl)pyrrolidines **3**, monoalkylated 4-halopyrrolidines **4** or **5** could be obtained stereospecifically after decomposition of the unstable dihaloselenuranes **16** and **17**.


## Introduction

We have previously observed that β-halopyrrolidines **4** (X = Cl) and **5** (X = Br) were obtained from amines **1b** to **1f**, at room temperature, when an excess of PhSeX (2.5 equiv.) (X = Cl, Br) was added[2] (Scheme 1, method $A_1$).




Scheme 1

In this second paper, we present a more complete study of this reaction, which has resulted in a new stereoselective preparation of *trans*-1,2-dialkyl-4-halopyrrolidines **4** and **5**. We also report the stereospecific two-step synthesis of the *cis* stereoisomers **4** and **5** from 1,2-dialkyl-4-(phenylselanylmethyl)azetidines *cis*-**2**, by ring expansion of (halomethyl)azetidines **14** (X = Cl) and **15** (X = Br). In addition, the isomers *trans*-**4** and *trans*-**5** were prepared by treatment of 1,2-dialkyl-4-(phenylselanyl)pyrrolidines *cis*-**3** with $SO_2Cl_2$ or $Br_2$, respectively.

## Results and Discussion

When using an excess of PhSeX (X = Cl, Br, I; 2.5 equiv.), we observed that selenium-induced cyclizations of **1a** ($R^1 = R^2 = H$)[1] and of **1g−1k** ($R^1$, $R^2 \neq H$)[2] always resulted in the same **2/3** mixture. In contrast, the α-substituted amines **1b−1f** ($R^2 = H$), when a large excess of PhSeX (X = Cl, Br) was added at room temp. under the same experimental conditions, afforded 10:90 *cis*/*trans* mixtures of β-halopyrrolidines **4** (X = Cl) or **5** (X = Br) . The β-halopyrrolidines **4b−4f** and **5b−5f** ($R^2 = H$) were obtained in good yields, and the *trans* isomers were easily isolated after chromatographic separation (Scheme 1; method $A_1$). PhSeI did not give β-iodopyrrolidines, and mixtures of azetidines **2** and pyrrolidines **3** were always obtained (Scheme 2). This must be the result of the absence of an equilibrium between **6(I)** and its thermodynamic addition product **7**. The corresponding adduct **7(Br)** has been characterized by $^{77}Se$ NMR.[1] Azetidine *cis*-**2e** ($R^1 = t$Bu, $R^2 = H$) and pyrrolidine *cis*-**3d** ($R^1 = i$Pr, $R^2 = H$) were separately treated with PhSeBr (1.5 equiv.) in MeCN containing $Na_2CO_3$. After hydrolysis, *cis*-**2e** and *cis*-**3d** were completely recovered. According to method $A_1$, the selenylated azetidines **2** and pyrrolidines **3** are not intermediates.

In the same work,[1] we showed that the azetidinium and pyrrolidinium salts **2(HX)** and **3(HX)** were formed in the

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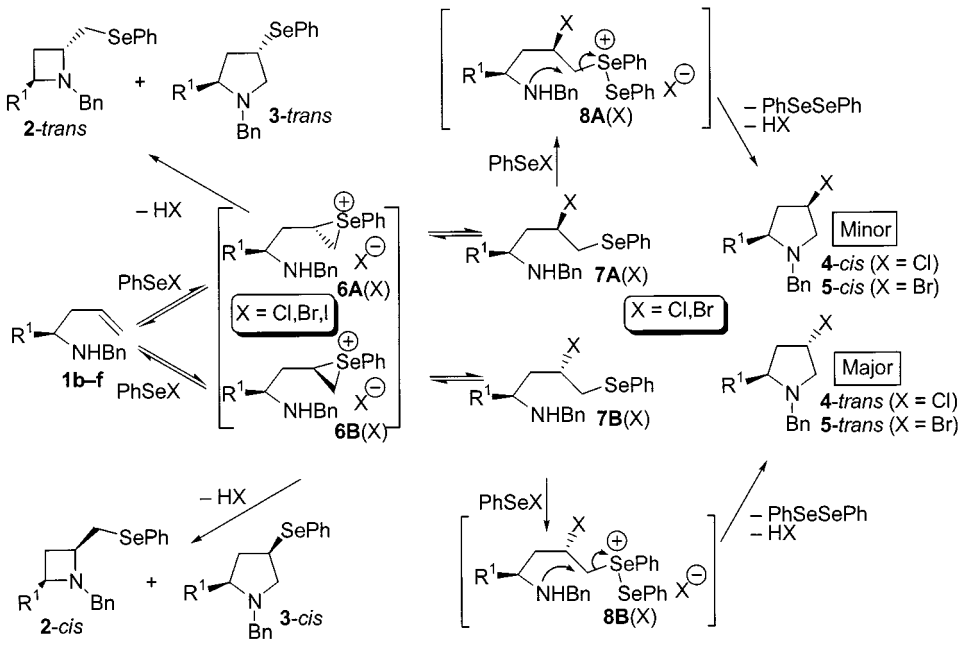



Scheme 2

absence of $Na_2CO_3$. We also observed that amines **1g−1k** ($R^1$, $R^2 \neq H$), on heating in $CH_3CN$, gave the corresponding β-halopyrrolidines **4** (X = Cl) or **5** (X = Br) after neutralisation, (Scheme 1, Table 1; method $A_2$). By the same procedure, the parent amine **1a** also afforded, after alkaline treatment, the unstable 1-benzyl-3-chloropyrrolidine **4a** or 1-benzyl-3-bromopyrrolidine **5a**. We suggested previously that, in the presence of $Na_2CO_3$, the NHBn or NBn(SePh) group could be the nucleophile in the cyclization of amines **1** to afford mixtures of azetidines **2** and pyrrolidines **3**.[1] Without an α-effect ($R^2$ = H), an excess of PhSeX (X = Cl, Br) must permit a fast selenophilic reaction with the thermodynamic addition products **7A/7B** to produce **8A/8B**. The selanylselenonium cation being an efficient leaving group,[3] the cyclization must occur more rapidly, with formation of the β-halopyrrolidines **4** (X = Cl) and **5** (X = Br) in diastereoisomeric ratios reflecting that of **7A/7B**. This mechanism is set out in Scheme 2 with NHBn as the nucleophilic centre, but we hoped that it could be replaced with the selenenamide function. In this case, the loss of PhSeX at the end of the reaction would give **4** or **5**. As a consequence of the geminal α-effect and whatever the nature of the nucleophile when two α-substituents were present ($R^2 \neq H$), the selenylated azetidines **2g−2k** were always isolated as the major products, in $CH_3CN$ at room temp. The geminal α-effect ($R^2 \neq H$) dramatically favoured the kinetic formation of the smallest heterocycle through a 4-*exo*-*trig* process,[1] and the β-halopyrrolidine could not be formed.

In the absence of $Na_2CO_3$, a large excess of PhSeX (X = Cl, Br) in refluxing $CH_3CN$ probably produced the selenenamide **9** ($R^1$, $R^2 \neq H$) and then the selanylselenonium halide **10**, which cyclized into (phenylselanyl)pyrrolidinium salt **11**. The presence of HX must allow the formation of **4(HCl)** or **5(HBr)**, as proposed for the PhSeX-induced isomerization of **2a(HX)** and **3a(HX)**.[1] Alkaline hydrolysis then afforded the β-halopyrrolidine **4** (X = Cl) or **5** (X = Br) in good yields (Scheme 3, Table 1; method $A_2$). By the same procedure, but without heating, **4a** and **5a** were prepared from the parent amine **1a**.

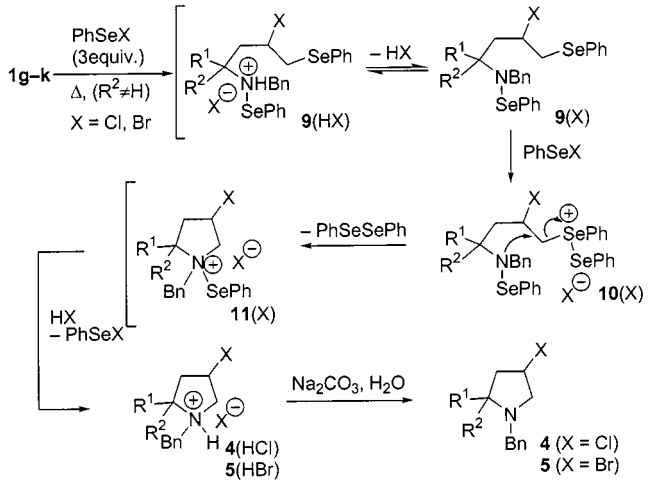
These results allow us to report a efficient new synthesis of *trans*-1,2-dialkyl-4-halopyrrolidines (method $A_1$) after separation of the minor *cis* isomers, and also of 1,2,2-trialkyl-4-halopyrrolidines (method $A_2$, Table 1).

The halogen affinity of phenylselenides is well known.[4] The Se-dibromo complexes are generally unstable and decompose in solution into PhSeBr and alkyl bromide,[5] and secondary alkyl phenylselenides have been prepared with inversion of configuration.[6] The more stable dichloroselenuranes decompose slowly in $CH_3CN$ or $CCl_4$, with formation of PhSeCl and alkyl chloride.[7,8] This two-step reaction allowed the synthesis of *vic*-dichloroalkanes,[7] 2-halocyclohexyl alcohols, nitriles, and amine derivatives,[8] α-chloroaldehydes,[9] α-chloroketones,[9,10] vinylic chlorides,[11] and vinylic and allylic acetates.[12] β-Chloro dichloroselenuranes have also been prepared by a regioselective anti-Markovnikov $PhSeCl_3$ addition to olefins.[13] $SO_2Cl_2$ treatment of phenylselenides was also efficient for access to Se−dichloro adducts.[1,14] Se−dihalo adducts (X = Cl, Br) derived from γ-phenylselanyl α,β-unsaturated esters were decomposed into α-halo-β,γ-unsaturated esters when PhSeX was trapped with ethyl vinyl ether.[15] This halogenation−rearrangement sequence provided a good method for the synthesis of diethyl 2-alkylidene-3-halosuccinates.[16] Additionally, $SO_2Cl_2$ or $Br_2$ treatment of propargylic phenylselenides afforded 1,3-dihalo-2-(phenylselanyl)-propene derivatives through the intermediate formation of haloallenes.[17]

Table 1. Stereocontrolled synthesis of β-chloropyrrolidines **4** and β-bromopyrrolidines **5**

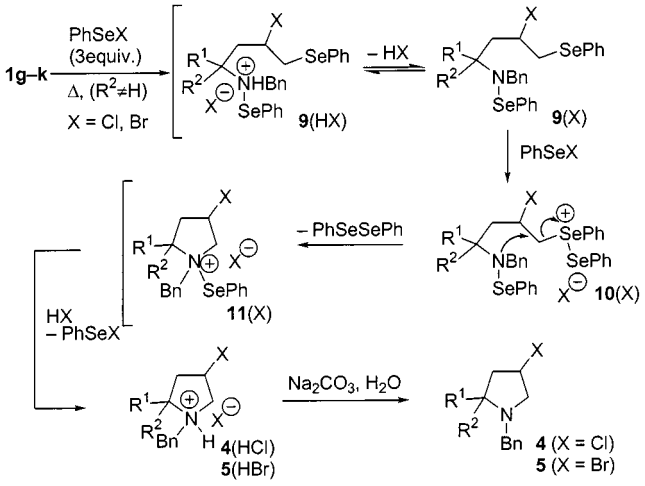
| Entry | β-Chloropyrrolidine **4** β-Bromopyrrolidine **5** | | | | Method $A_1$ ($R^2$ = H)[a] and $A_2$ ($R^2 \neq$ H) | Method B **2** → **14**,**15** → **4**,**5** *cis*-**2** ($R^2$ = H) → *cis*-**4**,**5** | | | Method C *cis*-**3** → *trans*-**4**,**5** |
|---|---|---|---|---|---|---|---|---|---|
| | No. | X | $R^1$ | $R^2$ | Yield (%) | No. | Yield (%) | Overall yield (%) | Yield (%) |
| 1 | 4a | Cl | H | H | –[b] | – | – | –[c] | –[c] |
| 2 | 5a | Br | H | H | –[b] | – | – | –[c] | –[c] |
| 3 | 4b | Cl | Me | H | 81 | – | – | – | 85 |
| 4 | 5b | Br | Me | H | 83 | – | – | – | 89 |
| 5 | 4c | Cl | Et | H | 79 | 14c | 78 | 70 | 83 |
| 6 | 5c | Br | Et | H | 78 | 15c | 67 | 58 | 77 |
| 7 | 4d | Cl | *i*Pr | H | 77 | 14d | 66 | 55 | 79 |
| 8 | 5d | Br | *i*Pr | H | 80 | 15d | 65 | 55 | 83 |
| 9 | 4e | Cl | *t*Bu | H | 85 | 14e | 75 | 68 | 83 |
| 10 | 5e | Br | *t*Bu | H | 72 | 15e | 68 | 60 | 72 |
| 11 | 4f | Cl | Ph | H | 75 | – | – | – | 78 |
| 12 | 5f | Br | Ph | H | 82 | – | – | – | 82 |
| 13 | 4g | Cl | Me | Me | 58 | 14g | 68 | 60 | – |
| 14 | 5g | Br | Me | Me | 52 | –[d] | –[d] | 85 | – |
| 15 | 4h | Cl | Ph | Me | 81[e] | 14h | 71 | 65[f] | – |
| 16 | 5h | Br | Ph | Me | – | –[d] | –[d] | 79[f] | – |
| 17 | 4i | Cl | Et | Et | 78 | 14i | 65 | 58 | – |
| 18 | 5i | Br | Et | Et | 80 | – | – | – | – |
| 19 | 4j | Cl | Et | Me | 78[g] | – | – | – | – |
| 20 | 4k | Cl | -$(CH_2)_5$- | | 80 | 14k | | 65 | – |
| 21 | 5k | Br | -$(CH_2)_5$- | | 41 | – | | – | – |

[a] 10:90 *cis*/*trans* mixture. [b] 18:82 mixture of **2a**/**3a** always formed. [c] Not isolated in pure form. [d] Fast decomposition. [e] 45:55 isomer mixture. [f] Stereochemistry not assigned. [g] 50:50 isomer mixture.

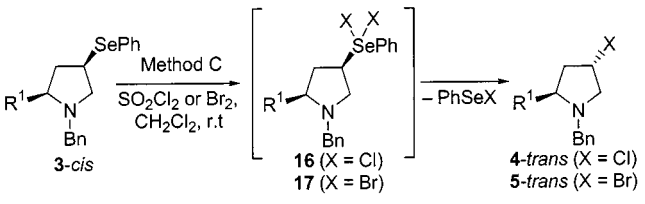



Scheme 3

In continuation of this work, we were interested in the halogenation of 2-(phenylselanylmethyl)azetidines **2** and 3-(phenylselanyl)pyrrolidines **3**. A crude sample of **2a** was treated with bromine (1 equiv.) in $CDCl_3$. The corresponding Se−dibromo complex **13a** decomposed immediately. After aqueous alkaline workup, the $^1H$ NMR spectrum revealed the formation of the (bromomethyl)azetidine **15a**. A slow rearrangement (100% conversion in 5 days at room temp.) into 1-benzyl-3-bromopyrrolidine **5a**[18,19] was then observed (Scheme 4). The 3-(phenylselanyl)pyrrolidine **3a** was also treated with bromine in hot $CCl_4$. Subsequent aqueous alkaline treatment afforded the unstable bromopyrrolidine **5a** in virtually quantitative yield (Scheme 5). Compound **3a** was subjected to the action of $SO_2Cl_2$, and the very unstable 1-benzyl-3-chloropyrrolidine **4a**[20] was obtained under the same conditions.




Scheme 4




Scheme 5

Pure samples of *cis*-2-monosubstituted azetidines **2c**, **2d**, and **2e**[1,2] were then treated with $SO_2Cl_2$ in hexane. The stable dichloroselenuranes **12c**, **12d**, and **12e** were quantitatively formed. These decomposed in refluxing $CCl_4$, the *cis*-(chloromethyl)azetidines **14c**, **14d**, and **14e** being isolated in correct yields. These compounds stereospecifically rearranged into *cis*-1,2-dialkyl 4-chloropyrrolidines **4c**, **4d**, and **4e**, respectively, on heating in $CH_3CN$ (Scheme 4, Table 1, method B). Analogously, bromine treatment of **2c**, **2d**, and **2e** (*cis*) gave stable dibromoselenuranes **13c**, **13d**, and **13e**, which then rearranged into *cis*-1,2-dialkyl-4-bromopyrrolidines **5c**, **5d**, and **5e** (Table 1).

The 2,2-disubstituted azetidines **2g**, **2h**, and **2k** were then subjected to the same halogen treatment. The unstable bromomethylazetidines **15g**, **15h**, and **15k**, were not isolated. The corresponding β-chloro and β-bromopyrrolidines **4** and **5** were directly formed in good yields (Table 1, method B).

The *cis* stereochemistry of **4c**, **4d**, **4e**, **5c**, **5d**, and **5e** was assigned with reference to the literature.[21] The stereospecific ring-enlargement of the (halomethyl)azetidines *cis*-**14** and *cis*-**15** into pyrrolidines *cis*-**4** and *cis*-**5** occurs as shown in Scheme 4. Similar rearrangements of (halomethyl)pyrrolidines into β-halopiperidines have been described.[22] Ring expansion to β-halopyrrolidines has also been observed.[21]

Some pyrrolidines *cis*-**3** ($R^2$ = H) have been isolated in a pure form.[1,2] Compounds **3b**, **3c**, **3d**, **3e**, and **3f** (*cis*) were treated with $SO_2Cl_2$ in $CH_2Cl_2$ at room temp. The corresponding unstable dichloroselenuranes **16** decomposed on heating. The *trans*-1,2-dialkyl-4-chloropyrrolidines **4b**, **4c**, **4d**, **4e**, and **4f** were isolated in good yields. A similar bromine treatment afforded the *trans*-1,2-dialkyl-4-bromopyrrolidines **5b**, **5c**, **5d**, **5e**, and **5f** in comparable yields (Scheme 5; Table 1, method C). In the two series, the loss of PhSeX occurred stereospecifically with inversion of configuration.

## Conclusion

We report a new synthesis of 1,2-dialkyl-4-halopyrrolidines **4** (X = Cl) and **5** (X = Br) by a selenium-induced cyclization of *N*-benzyl-homoallylamines **1b−1f**, achieved at room temperature by use of an excess of PhSeX (2.5 equiv.) in $CH_3CN$ containing $Na_2CO_3$. The *trans* isomer was formed stereoselectively (*cis*/*trans* = 10:90) and easily isolated (Method $A_1$). Under the same conditions, the selenenylated azetidines **2g−2k** were always obtained as the major kinetic products, as a consequence of the geminal α-effect ($R^1$, $R^2 \neq$ H). In the absence of $Na_2CO_3$, the shifted equilibrium from the seleniranium salt **6** towards the thermodynamic addition product **7** must explain a subsequent selenophilic reaction with PhSeX, allowing access to 1,2,2-trialkyl-4-halopyrrolidines **4g−4k** (X = Cl) or **5g−5i** (X = Br) after neutralisation of the corresponding HX salts (Method $A_2$). The unstable parent compounds **4a** and **5a** could also be obtained at room temp. by the same route.

A stereospecific two-step sequence for the preparation of 1,2-dialkyl-4-halopyrrolidines *cis*-**4** and *cis*-**5** from azetidines *cis*-**2**, by way of the (halomethyl)azetidines *cis*-**14** (X = Cl) or *cis*-**15** (X = Br), is also reported (Method B). The 1,2,2-trialkyl-4-halopyrrolidines **4** and **5** were prepared in the same way. Halopyrrolidines *trans*-**4** and *trans*-**5** ($R^2$ = H) were stereospecifically synthesised by halogen treatment of 1,2-dialkyl-4-(phenylselanyl)pyrrolidines *cis*-**3** ($R^2$ = H) (Method C). The low proportions of 2,2-disubstituted (phenylselanyl)pyrrolidines **3** prevent access to the corresponding halopyrrolidines **4g−4k** and **5g−5k** in this way. Numerous patents and some articles[23] have described the synthesis, chemical transformations and biological activity of 1-alkyl 3-chloropyrrolidines. Our work now allows study of the *cis* and *trans* stereoisomers of 1,2-dialkyl-4-halopyrrolidines.

We are at present interested in the reactivity of the (halomethyl)azetidines **14** and **15**. An asymmetric version of this new synthesis of β-halopyrrolidine derivatives is also under investigation.

## Experimental Section

**General:** Solvents were purified by conventional methods prior to use. TLC was performed on Merck 60F-250 silica gel plates, and column chromatography over SI 60 silica gel (230−240 mesh). Mps were taken on a Kofler apparatus and were uncorrected. Elemental analyses were carried out on a Carlo Erba EA 1100 analyser. NMR spectra were recorded on a Bruker DPX 300 spectrometer operating at 300 MHz for hydrogen and 75.4 MHz for carbon. This probe was equipped with pulsed-field (z) gradients. Chemical shifts (δ) are expressed in ppm relative to TMS for $^1$H and $^{13}$C nuclei; coupling constants (*J*) are given in Hertz; coupling multiplicities are reported with conventional abbreviations.

The homoallylamines **1a−1k**, *N*-benzyl(phenylselanylmethyl)azetidines **2a**, **2c**, **2d**, **2e**, **2g**, **2h**, and **2k** and *N*-benzyl(phenylselanyl)pyrrolidines **3a−3f** were described in the preceding paper.[1]

**A) Treatment of Homoallylic Amines 1 with PhSeX in Excess. Method $A_1$. General Procedure (for Amines 1b to 1f):** The amine **1** (3 mmol), in $CH_3CN$ (10 mL) containing sodium carbonate (600 mg), was treated dropwise at room temperature with a solution of PhSeX (X = Cl or Br; 2.5 equiv.) in the same solvent (30 mL). The mixture was stirred for 10 h and then treated with an aqueous solution of NaCl (50 mL). The organic layer was washed with water, dried and concentrated. The oily residue was chromatographed on silica gel. Diphenyldiselenide was removed first, by hexane elution. A 90:10 hexane/$CH_2Cl_2$ mixture then allowed the separation of the minor *cis*-2-alkyl-4-halopyrrolidine **4** (or **5**). The *trans* isomer was then isolated by elution with a 60:40 mixture of the same solvents. The overall yields are given in the Table 1. The isolated *cis*-β-halopyrrolidine was always contaminated with the major *trans* isomer.

***trans*-1-Benzyl-4-chloro-2-methylpyrrolidine (4b):** Oil. 0.402 g, 64% yield. $^1$H NMR: δ = 1.17 (d, 3 H, *J* = 6.0 Hz, Me), 2.01 (m, 1 H, 3-H), 2.15 (m, 1 H, 3-H), 2.47 (dd, *J* = 6.1, 10.6 Hz, 1 H, 5-H), 2.87 (m, 1 H, 2-H), 3.27 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 3.40 (dd, *J* = 6.6, 10.6 Hz, 1 H, 5-H), 4.04 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 4.27 (m,1 H, 4-H), 7.18−7.30 (m, 5 H, Ph). $^{13}$C NMR: δ = 18.5 (Me), 44.0 (*C*-3), 54.2 (*C*-4), 57.4 (*C*$H_2$Ph), 57.5 (*C*-2), 63.1 (*C*-5), 126.6, 127.9, 128.3, 138.7. Anal. Calcd. for $C_{12}H_{16}ClN$: calcd. C 68.72, H 7.69, N 6.68; found C 69.04, H 7.81, N 6.93.

***trans*-1-Benzyl-4-chloro-2-ethylpyrrolidine (4c):** Oil. 0.410 g, 61% yield. $^1$H NMR: δ = 0.92 (t, *J* = 7.4 Hz, 3 H, Me), 1.37 (m, 1 H, C*H*$_2$Me), 1.76 (m, 1 H, C*H*$_2$Me), 2.06 (m, 1 H, 3-H), 2.16 (m, 1 H, 3-H), 2. 48 (dd, *J* = 6.4, 10.5 Hz, 1 H, 5-H), 2.78 (m, 1 H, 2-H), 3.31 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 3.37 (dd, *J* = 6.4, 10.5 Hz, 1 H, 5-H), 4.05 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 4.26 (m, 1 H, 4-H), 7.20−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 9.8 (Me), 25.7 (*C*H$_2$Me), 41.1 (*C*-3), 54.5 (*C*-4), 57.9 (*C*H$_2$Ph), 63.0 (*C*-5), 63.7 (*C*-2), 126.7, 128.0, 128.4, 138.7. $C_{13}H_{18}ClN$: calcd. C 69.78, H 8.11, N 6.26; found C 70.12, H 8.22, N 6.35.

***trans*-1-Benzyl-4-chloro-2-isopropylpyrrolidine (4d):** Oil. 0.484 g, 68% yield. $^1$H NMR: δ = 0.91(dd, 6 H, *J* = 1.9, 6.9 Hz, Me), 1.95 (m, 2 H, 3-H and C*H*Me$_2$), 2.14 (m, 1 H, 3-H), 2.48 (dd, 1 H, *J* = 6.6, 10.2 Hz, 5-H), 2.83 (m, 1 H, 2-H), 3.26−3.40 (m, 2 H, 5-H and C*H*$_2$Ph), 4.04 (d, 1 H, $J_{AB}$ = 13.2 Hz, C*H*$_2$Ph), 4.21 (m, 1 H, 4-H), 7.18−7.34 (m, 5 H, Ph). $^{13}$C NMR: δ = 20.0 (Me), 28.4 (*C*HMe$_2$), 36.6 (*C*-3), 55.0 (*C*-4), 58.9 (*C*H$_2$Ph), 62.5 (*C*-5), 68.0 (*C*-2), 127.3, 128.3, 128.8, 138.7. $C_{14}H_{20}ClN$: calcd. C 70.72, H 8.48, N 5.89; found C 7068, H 8.37, N 5.92.

***trans*-1-Benzyl-2-*tert*-butyl-4-chloropyrrolidine (4e):** Oil. 0.540 g, 71% yield. $^1$H NMR: δ = 0.90 (s, 9 H, *t*Bu), 2.13−2.35 (m, 2 H, 3-H), 2.65 (dd, *J* = 6.4, 10.5 Hz, 1 H, 5-H), 3.01 (m,1 H, 2-H), 3.95 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 4.03 (dd, *J* = 6.1, 10.5 Hz, 1 H, 5-H), 4.08 (d,1 H, $J_{AB}$ = 13.2 Hz, Bn), 4.29 (m, 1 H, 4-H), 7.18−7.30 (m, 5 H, Ph). $^{13}$C NMR: δ = 26.0 (Me), 41.30 (*C*-3), 54.7 (*C*-4), 59.8 (*C*H$_2$Ph), 62.8 (*C*-5), 69.6 (*C*-2), 127.4, 128.3, 128.9, 138.7. $C_{15}H_{22}ClN$: calcd. C 71.55, H 8.81, N 5.56; found C 71.48, H 8.64, N 5.89.

***trans*-1-Benzyl-4-chloro-2-phenylpyrrolidine (4f):** Oil. 0.524 g, 65% yield. $^1$H NMR: δ = 2.20−2.48 (m, 2 H, 3-H), 2.59 (dd, *J* = 5.8, 10.6 Hz, 1 H, 5-H), 3.20 (d, 1 H, $J_{AB}$ = 13.1 Hz, C*H*$_2$Ph), 3.60 (dd, *J* = 6.6, 10.6 Hz, 1 H, 5-H), 3.82−3.90 (m, 2 H, 2-H and C*H*$_2$Ph), 4.40 (m, 1 H, 4-H), 7.20−7.60 (m, 10 H, Ph). $^{13}$C NMR: δ = 46.4 (*C*-3), 54.9 (*C*-4), 57.6 (*C*H$_2$Ph), 62.8 (*C*-5), 67.3 (*C*-2), 127.5, 128.3, 128.5, 138.8. $C_{17}H_{18}ClN$: calcd. C 75.12, H 6.75, N 5.15; found C 75.38, H 6.81, N 4.95.

***trans*-1-Benzyl-4-bromo-2-methylpyrrolidine (5b):** Oil. 0.440 g, 58% yield. $^1$H NMR: δ = 1.18 (d, *J* = 6.0 Hz, 3 H, Me), 2.08−2.37 (m, 2 H, 3-H), 2.65 (dd, *J* = 6.5, 10.7 Hz, 1 H, 5-H), 2.89 (m, 1 H, 2-H), 3.28 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 3.46 (dd, *J* = 6.8, 10.7 Hz, 1 H, 5-H), 4.05 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 4.28 (m, 1 H, 4-H), 7.18−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 18.6 (Me), 43.9 (*C*-4), 44.6 (*C*-3), 57.5 (*C*-2), 57.9 (*C*H$_2$Ph), 63.6 (*C*-5), 126.8, 128.0, 128.5, 138.7. $C_{12}H_{16}BrN$: calcd. C 56.69, H 6.34, N 5.51; found C 56.80, H 6.26, N 5.93.

***trans*-1-Benzyl-4-bromo-2-ethylpyrrolidine (5c):** Oil. 0.442 g, 55% yield. $^1$H NMR: δ = 0.91 (t, *J* = 7.4 Hz, 3 H, Me), 1.28−1.50 (m, 1 H, C*H*$_2$Me), 1.65−1.85 (m, 1 H, C*H*$_2$Me), 2.07−2.36 (m, 2 H, 3-H), 2.65 (dd, *J* = 6.8, 10.6 Hz, 1 H, 5-H), 2.80 (m, 1 H, 2-H), 3.31 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 3.44 (dd, *J* = 6.3, 10.6 Hz, 1 H, 5-H), 4.05 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 4.25 (m, 1 H, 4-H), 7.18−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 10.0 (Me), 25.8 (*C*H$_2$Me), 41.7 (*C*-3), 44.1 (*C*-4), 58.0 (*C*H$_2$Ph), 63.4 (*C*-5), 64.2 (*C*-2), 127.0, 128.2, 128.6, 138.4. $C_{13}H_{18}BrN$: calcd. C 58.21, H 6.76, N 5.22; found C 58.28, H 6.93, N 5.62.

***trans*-1-Benzyl-4-bromo-2-isopropylpyrrolidine (5d):** Oil. 0.521 g, 61% yield. $^1$H NMR: δ = 0.92 (d, *J* = 6.9 Hz, 6 H, Me), 1.97 (m, 1 H, C*H*Me$_2$), 2.00−2.30 (m, 2 H, 3-H), 2.64 (dd, *J* = 7.1, 10.4 Hz, 1 H, 5-H), 2.84 (m, 1 H, 2-H), 3.34 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 3.39 (m, 1 H, 5-H), 4.05 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 4.20 (m, 1 H, 4-H), 7.18−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 15.7 (Me), 20.0 (Me), 28.6 (*C*HMe$_2$), 37.0 (*C*-3), 44.8 (*C*-4), 58.7 (*C*H$_2$Ph), 63.4 (*C*-5), 68.1 (*C*-2), 127.3, 128.5, 128.7, 138.6. $C_{14}H_{20}BrN$: calcd. C 59.56, H 7.14, N 4.96; found C 59.27, H6.94, N 5.12.

***trans*-1-Benzyl-4-bromo-2-*tert*-butylpyrrolidine (5e):** Oil. 0.486 g, 55% yield. $^1$H NMR: δ = 0.96 (s, 9 H, *t*Bu), 2.08−2.24 (m, 2 H, 3-H), 2.77 (dd, *J* = 4.2, 11.9 Hz, 1 H, 5-H), 3.03 (m, 1 H, 2-H), 3.21 (dd, *J* = 4.4, 11.9 Hz, 1 H, 5-H), 3.98 (d, 1 H, $J_{AB}$ = 14.2 Hz, Bn), 4.13 (d, 1 H, $J_{AB}$ = 14.2 Hz, Bn), 4.33 (m, 1 H, 4-H), 7.20−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 26.7 (Me), 42.4 (*C*-3), 44.3 (*C*-4), 57.7 (*C*H$_2$Ph), 62.9 (*C*-5), 65.1 (*C*-2), 127.8, 128.8, 129.3, 138.7. $C_{15}H_{22}BrN$: calcd. C 60.81, H 7.48, N 4.73; found C 60.75, H 7.38, N 4.68.

***trans*-1-Benzyl-4-bromo-2-phenylpyrrolidine (5f):** Oil. 0.583 g, 62% yield. $^1$H NMR: δ = 2.35−2.68 (m, 2 H, 3-H), 2.86 (dd, *J* = 6.3, 10.8 Hz, 1 H, 5-H), 3.27 (d, 1 H, $J_{AB}$ = 13.0 Hz, Bn), 3.73 (dd, *J* = 6.6, 10.8 Hz, 1 H, 5-H), 3.94 (d, 1 H, $J_{AB}$ = 13.0 Hz, Bn), 3.94 (m, 1 H, 2-H), 4.45 (m, 1 H, 4-H), 7.25−7.60 (m, 10 H, Ph). $^{13}$C NMR: δ = 44.4 (*C*-4), 46.9 (*C*-3), 57.6 (*C*H$_2$Ph), 63.3 (*C*-5), 67.7 (*C*-2), 127.2, 127.6, 128.4, 128.7, 128.8, 129.1, 138.9, 141.9. $C_{17}H_{18}BrN$: calcd. C 64.56, H 5.74, N 4.43; found C 64.18, H 5.65, N 4.73.

**Method A$_2$. General Procedure (for Amines 1g to 1k):** A solution of PhSeX (X = Cl or Br, 3 mmol) in anhydrous $CH_3CN$ (10 mL) was slowly added to amine **1** (**1g** to **1k**, 1 mmol) dissolved in the same solvent (5 mL). The mixture was heated at reflux for 18 h. After this had cooled, sodium carbonate (0.2 g) and water (15 mL) were added. The aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL) and the organic layers were dried and concentrated under reduced pressure. The oily residue was chromatographed on silica gel. After elimination of PhSeSePh, the halopyrrolidine **4** (or **5**) was eluted with a 80:20 mixture of cyclohexane/$CH_2Cl_2$.

The simple halopyrrolidines **4a**[20] and **5a**[18,19] ($R^1$ = $R^2$ = H) were formed without heating. Their instability, especially during silica gel chromatography, prevented their isolation in pure form.

**1-Benzyl-3-chloropyrrolidine (4a):**[20] $^1$H NMR: δ = 1.99−2.15 (m, 1 H, 4-H), 2.32−2.52 (m, 1 H, 4-H), 2.60−2.84 (m, 3 H, 2-H and 5-H), 3.11 (dd, *J* = 6.3, 10.7 Hz, 1 H, 2-H), 3.65 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 3.73 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 4.38 (m, 1 H, 3-H), 7.25−7.36 (m, 5 H, Ph). $^{13}$C NMR: δ = 35.8 (*C*-4), 52.4 (*C*-5), 56.2 (*C*-3), 59.9 (*C*H$_2$Ph), 63.1 (*C*-2), 127.1, 128.3, 128.7, 131.4.

**1-Benzyl-4-chloro-2,2-dimethylpyrrolidine (4g):** Oil. 0.128 g, 58% yield. $^1$H NMR: δ = 1.14 (s, 3 H, Me), 1.26 (s, 3 H, Me), 2.06 (dd, *J* = 4.8, 13.8 Hz, 1 H, 3-H), 2.35 (dd, *J* = 8.6, 13.8 Hz, 1 H, 3-H), 2.86 (dd, *J* = 5.0, 10.6 Hz, 1 H, 5-H), 3.14 (dd, *J* = 7.3, 10.6 Hz, 1 H, 5-H), 3.58 (s, 2 H, Bn), 4.32 (m, 1 H, 4-H), 7.16−7.40 (m, 5 H, Ph). $^{13}$C NMR: δ = 23.9 (Me), 24.5 (Me), 51.5 (*C*H$_2$Ph), 52.3 (*C*-3), 54.4 (*C*-4), 60.7 (*C*-5), 127.2, 128.6. $C_{13}H_{18}ClN$: calcd. C 69.78, H 8.11, N 6.26; found C 69.86, H 8.48, N 5.97.

**1-Benzyl-4-chloro-2-methyl-2-phenylpyrrolidine (4h):** Oil. 0.186 g, 65% yield. Mixture of *cis* and *trans* isomers (55:45). *cis* isomer: stereochemistry assigned by NOESY (Me and Cl *trans*). $^1$H NMR: δ = 1.45 (s, 3 H, Me), 2.42 (dd, *J* = 5.1, 14.1 Hz, 1 H, 3-H), 2.54 (dd, *J* = 7.7, 14.1 Hz, 1 H, 3-H), 3.05 (dd, *J* = 6.6, 11.5 Hz, 1 H, 5-H), 3.25 (m, 2 H, 5-H and C*H*$_2$Ph), 3.63 (d, 1 H, $J_{AB}$ = 13.5 Hz, C*H*$_2$Ph), 4.50 (m, 1 H, 4-H), 7.27−7.45 (m, 8 H), 7.75−7.82 (m, 2 H). $^{13}$C NMR: δ = 16.5 (Me), 51.0 (*C*-3), 53.3 (*C*H$_2$Ph), 54.5 (*C*-4), 58.2 (*C*-5), 65.2 (*C*-2), 125.2, 125.5, 125.7, 126.9, 127.2, 127.4, 127.8, 138.6. $C_{18}H_{20}ClN$: calcd. C 75.64, H 7.05, N 4.90; found C 75.32, H 7.01, N 5.10.

**1-Benzyl-4-chloro-2,2-diethylpyrrolidine (4i):** Oil. 0.120 g, 48% yield. $^1$H NMR: δ = 0.81 (t, *J* = 7.3 Hz, 3 H, Me), 0.88 (t, *J* = 7.3 Hz, 3 H, Me), 1.28−1.62 (m, 4 H, C*H*$_2$Me), 1.95 (dd, *J* = 6.1, 13.9 Hz, 1 H, 3-H), 2.18 (dd, *J* = 8.2, 13.9 Hz, 1 H, 3-H), 2.74 (dd, *J* = 5.9, 10.0 Hz, 1 H, 5-H), 3.01 (dd, *J* = 6.6, 10.0 Hz, 1 H, 5-H), 3.48 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 3.56 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.14 (m, 1 H, 4-H), 7.10−7.25 (m, 5 H, Ph). $^{13}$C NMR: δ = 9.2 (Me), 9.5 (Me), 27.7 (*C*H$_2$Me), 28.3 (*C*H$_2$Me), 43.4 (*C*-3), 51.3 (*C*H$_2$Ph), 54.9 (C-4), 59.9 (*C*-5), 66.2 (*C*-2), 127.2, 128.5, 128.7. $C_{15}H_{22}ClN$: calcd. C 71.55, H 8.81, N 5.56; found C 71.17, H 8.49, N 5.62.

**1-Benzyl-4-chloro-2-ethyl-2-methylpyrrolidine (4j):** Oil. 0.161 g, 58% yield (mixture of *cis* and *trans* isomers 50:50). $^1$H NMR: δ = 1.14 (s, 3 H), 1.26 (s, 3 H), 2.06 (dd, *J* = 4.8, 13.8 Hz, 1 H), 2.35 (dd, *J* = 8.6, 13.8 Hz, 1 H), 2.86 (dd, *J* = 5.0, 10.6 Hz, 1 H), 3.14 (dd, *J* = 7.3, 10.6 Hz, 1 H), 3.58 (s, 2 H), 4.32 (m, 1 H), 7.16−7.40 (m, 5 H). $^{13}$C NMR: δ = 23.9, 24.5, 37.7, 51.5 (*C*-3), 52.3 (*C*H$_2$Ph), 54.4 (*C*-4), 60.7 (*C*-5), 127.2, 128.6. $C_{14}H_{20}ClN$: calcd. C 70.72, H 8.48, N 5.89; found C 69.86, H 8.48, N 5.97.

**Spiro[cyclohexane-2(1-benzyl-4-chloropyrrolidine)] (4k):** Oil. 0.179 g, 68% yield. $^1$H NMR: δ = 1.00−1.85 (m, 10 H, $(CH_2)_5$], 2.08 (dd, *J* = 4.9, 14.0 Hz, 1 H, 3-H), 2.37 (dd, *J* = 8.5, 14.0 Hz, 1 H, 3-H), 2.87 (dd, *J* = 5.3, 10.3 Hz, 1 H, 5-H), 3.13 (dd, *J* = 6.7, 10.3 Hz, 1 H, 5-H), 3.60 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 3.70 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 4.29 (m, 1 H, 4-H), 7.18−7.36 (m, 5 H, Ph). $^{13}$C NMR: δ = 22.9, 23.2, 24.9, 31.6, 32.7 [(*C*H$_2$)$_5$], 44.9 (*C*-3), 50.3 (*C*H$_2$Ph), 54.4 (*C*-4), 58.4 (*C*-5), 63.1 (*C*-2), 126.1, 127.3, 128.6, 136.1. $C_{16}H_{22}ClN$: calcd. C 72.84, H 8.40, N 5.31; found C 73.19, H 8.02, N 5.51.

**1-Benzyl-3-bromopyrrolidine (5a):**[18,19] Oil. $^1$H NMR: δ = 2.15−2.30 (m, 1 H, 4-H), 2.42−2.61 (m, 1 H, 4-H), 2.72−2.80 (m, 2 H, 5-H), 2.89 (dd, 1 H, *J* = 4.8.11.0 Hz, 2-H), 3.24 (dd, *J* = 6.3, 11.0 Hz, 1 H, 2-H), 3.69 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 3.77 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 4.39 (m, 1 H, 3-H), 7.30−7.37 (m, 5 H, Ph). $^{13}$C NMR: δ = 35.3 (*C*-4), 44.5(*C*-3), 51.6 (*C*H$_2$Ph), 58.9 (*C*-5), 62.3 (*C*-2), 126.4, 127.8, 128.2, 136.5.

**1-Benzyl-4-bromo-2,2-dimethylpyrrolidine (5g):** Oil. 0.145 g, 55% yield. $^1$H NMR: δ = 1.09 (s, 3 H, Me), 1.23 (s, 3 H, Me), 2.18 (dd, *J* = 5.4, 14.0 Hz, 1 H, 3-H), 2.40 (dd, *J* = 8.5, 14.0 Hz, 1 H, 3-H), 2.95 (dd, *J* = 5.4, 10.9 Hz, 1 H, 5-H), 3.13 (dd, *J* = 7.1, 10.9 Hz, 1 H, 5-H), 3.55 (s, 2 H, C*H*$_2$Ph), 4.28 (m, 1 H, 4-H), 7.20−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 23.4 (Me), 24.0 (Me), 43.0 (*C*-4), 51.3 (*C*H$_2$Ph), 51.7 (*C*-3), 60.5 (*C*-5), 67.0 (*C*-2), 126.9, 128.2. $C_{13}H_{18}BrN$: calcd. C 58.21, H 6.76, N 5.22; found C 57.98, H 7.03, N 5.60.

**1-Benzyl-4-bromo-2-methyl-2-phenylpyrrolidine (5h):** Oil. 0.208 g, 64% yield. Mixture of *cis*/*trans* isomers: 55:45. *cis* isomer: Stereochemistry assigned by NOESY (Me and Br *trans*). $^1$H NMR: δ = 1.45 (s, 3 H, Me), 2.60 (d, *J* = 6.6 Hz, 2 H, 3-H), 3.13 (dd, *J* = 6.8, 11.6 Hz, 1 H, 5-H), 3.26 (d, 1 H, $J_{AB}$ = 13.7 Hz, Bn), 3.39 (dd, *J* = 2.4, 11.6 Hz, 1 H, 5-H), 3.65 (d, 1 H, $J_{AB}$ = 13.7 Hz, Bn), 4.52 (m, 1 H, 4-H), 7.12−7.42 (m, 8 H), 7.75−7.79 (m, 2 H). $^{13}$C NMR: δ = 17.5 (Me), 44.8 (*C*-4), 52.0 (*C*H$_2$Ph), 54.8 (*C*-3), 59.8 (*C*-5), 66.4 (*C*-2), 127.0, 127.2, 128.3, 128.7, 140.0, 146.3. $C_{18}H_{20}BrN$: calcd. C 65.45, H 6.10, N 4.24; found C 65.82, H 4.31, N 4.55.

**1-Benzyl-4-bromo-2,2-diethylpyrrolidine (5i):** Oil. 0.124 g, 44% yield. $^1$H NMR: ($CDCl_3$): δ = 0.92 (t, *J* = 7.4 Hz, 3 H, Me), 0.98 (t, *J* = 7.4 Hz, 3 H, Me), 1.40−1.70 (m, 4 H, C*H*$_2$Me), 2.12 (dd, *J* = 6.8, 14.1 Hz, 1 H, 3-H), 2.37 (dd, *J* = 8.3, 14.1 Hz, 1 H, 3-H), 2.95 (dd, *J* = 6.6, 10.1 Hz, 1 H, 5-H), 3.15 (dd, *J* = 6.6, 10.1 Hz, 1 H, 5-H), 3.59 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 3.70 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.25 (m, 1 H, 4-H), 7.20−7.40 (m, 5 H, Ph). $^{13}$C NMR: δ = 9.0 (Me), 9.5 (Me), 27.7 (*C*H$_2$Me), 28.3 (*C*H$_2$Me), 44.1 (*C*-3), 44.6 (*C*-4), 51.2 (*C*H$_2$Ph), 60.3 (*C*-5), 66.5 (*C*-2), 127.2, 128.5, 128.7. $C_{15}H_{22}BrN$: calcd. C 60.81, H 7.48, N 4.73; found C 60.62, H 7.20, N 4.36.

**Spiro Compound 5k:** Oil. 0.124 g, 41% yield. $^1$H NMR: δ = 0.96−1.85 (m, 10 H, $(CH_2)_5$], 2.23 (dd, *J* = 5.3, 14.2 Hz, 1 H, 3-H), 2.46 (dd, *J* = 8.4, 14.2 Hz, 1 H, 3-H), 2.98 (dd, *J* = 5.8, 10.5 Hz, 1 H, 5-H), 3.16 (dd, *J* = 6.6, 10.5 Hz, 1 H, 5-H), 3.61(d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 3.71 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 4.30 (m, 1 H, 4-H), 7.18−7.38 (m, 5 H, Ph). $^{13}$C NMR: δ = 23.8, 24.1, 25.8, 32.8, 33.7 [(*C*H$_2$)$_5$], 43.9 (*C*-4), 46.4 (*C*-3), 51.2 (*C*H$_2$Ph), 59.7 (*C*-5), 66.8 (*C*-2), 126.8, 128.1, 128.2, 129.0, 131.3. $C_{16}H_{22}BrN$: calcd. C 62.34, H 7.19, N 4.54; found C 62.64, H 7.05, N 4.36.

**B) Halogenation of (Phenylselanylmethyl)azetidines 2. a) Preparation of the (Chloromethyl)azetidines 14:** $SO_2Cl_2$ (200 mg, 1.5 mmol) in heptane (5 mL) was slowly added at room temp. to a solution of azetidine **2** (1 mmol) in the same solvent (10 mL). The crystalline dichloro adduct **12** was immediately formed, and was separated and decomposed by heating for 1 h in $CCl_4$ (10 mL). The reaction was treated with diluted aq. NaOH and the aqueous phase was extracted with $CH_2Cl_2$. The organic layers were washed with water and dried. After elimination of the solvents, the oily product was chromatographed on silica gel (elution: $CH_2Cl_2$/heptane, 20:80). The 2-subtituted 4-(chloromethyl)azetidines **14c**, **14d** and **14e** and the 2,2-disubstituted azetidines **14g**, **14h** and **14k** were isolated in pure form.

***cis*-1-Benzyl-2-(chloromethyl)-4-ethylazetidine (14c):** Oil. 0.172 g, 78% yield. $^1$H NMR: δ = 0.66−0.73 (m, 3 H, Me), 1.18−1.45 (m, 3 H, 3-H and C*H*$_2$Me), 2.19 (m, 1 H, 3-H), 2.86 (m, 1 H, 4-H), 3.06−3.17 (m, 3 H, 2-H and C*H*$_2$Cl), 3.54 (d, 1 H, $J_{AB}$ = 12.7 Hz, Bn), 3.66 (d, 1 H, $J_{AB}$ = 12.7 Hz, Bn), 7.14−7.26 (m, 5 H, Ph). $^{13}$C NMR: δ = 8.2 (Me), 27.2 (*C*-3), 28.2 (*C*H$_2$Me), 47.2 (*C*H$_2$Cl), 61.0 (*C*H$_2$Ph), 61.5 (*C*-2), 62.8 (*C*-4), 126.1, 127.2, 128.2. $C_{13}H_{18}ClN$: calcd. C 69.78, H 8.11, N 6.26; found C 69.95, H 8.31, N 6.63.

***cis*-1-Benzyl-2-(chloromethyl)-4-isopropylazetidine (14d):** Oil. 0.157 g, 66% yield. $^1$H NMR: δ = 0.80 (d, *J* = 9.2 Hz, 3 H, Me), 0.84 (d, *J* = 9.2 Hz, 3 H, Me), 1.44−1.66 (m, 2 H, 3-H and C*H*Me$_2$), 2.13−2.26 (m, 1 H, 3-H), 2.76 (m, 1 H, 4-H), 2.97−3.15 (m, 3 H, 2-H and C*H*$_2$Cl), 3.49 (d, 1 H, $J_{AB}$ = 12.8 Hz, Bn), 3.85 (d, 1 H, $J_{AB}$ = 12.8 Hz, Bn), 7.15−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 17.4 (Me), 18.7 (Me), 25.8 (*C*-3), 33.8 (*C*HMe$_2$), 48.0 (*C*H$_2$Cl), 61.9 (*C*-2), 62.5 (*C*H$_2$Ph), 68.0 (*C*-4), 127.1, 128.1, 129.0. $C_{14}H_{20}BrN$: calcd. C 70.72, H 8.48, N 5.89; found C 70.83, H 8.35, N 5.97.

***cis*-1-Benzyl-2-*tert*-butyl-4-(chloromethyl)azetidine (14e):** Oil. 0.185 g, 75% yield. $^1$H NMR: δ = 0.80 (s, 9 H, *t*Bu), 1.55 (m, 1 H, 3-H), 2.04 (m, 1 H, 3-H), 2.74−2.84 (m, 2 H, 2-H and 4-H), 2.98−3.06 (m, 2 H, $CH_2Cl$), 3.37 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 3.86 (d, 1 H, $J_{AB}$ = 13.1 Hz, Bn), 7.15−7.27 (m, 5 H, Ph). $^{13}$C NMR: δ = 22.4 (*C*-3), 24.8 (Me), 32.4 (*C*Me$_3$), 46.8 (*C*H$_2$Cl), 61.0 (*C*-4), 62.4 (*C*H$_2$Ph), 70.0 (*C*-2), 127.1, 127.8, 128.1, 138.3. $C_{15}H_{22}ClN$: calcd. C 71.55, H 8.81, N 5.56; found C 71.32, H 5.43, N 5.27.

**1-Benzyl-2-(chloromethyl)-4,4-dimethylazetidine (14g):** Oil. 0.150 g, 68% yield. $^1$H NMR: δ = 1.04 (s, 3 H, Me), 1.18 (s, 3 H, Me), 1.66 (dd, *J* = 8.0, 10.3 Hz, 1 H, 3-H), 1.92 (dd, *J* = 7.4, 10.3 Hz, 1 H, 3-H), 3.04−3.15 (m, 2 H, $CH_2Cl$), 3.29 (m, 1 H, 2-H), 3.46 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 3.66 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 7.06−7.30 (m, 5 H, Ph). $^{13}$C NMR: δ = 21.5 (Me), 31.1 (Me), 37.7

(*C*-3), 49.1 (*C*$H_2$Cl), 54.6 (*C*$H_2$Ph), 60.7 (*C*-4), 61.7 (*C*-2), 127.3, 128.5, 128.7.129.2. $C_{13}H_{18}ClN$: calcd. C 69.78, H 8.11, N 6.26; found C 69.88, H 8.27, N 6.31.

**1-Benzyl-2-(chloromethyl)-4-methyl-4-phenylazetidine (14h):** Oil. 0.201 g, 71% yield; Stereochemistry not assigned. $^1$H NMR: δ = 1.57 (s, 3 H, Me), 1.94 (dd, *J* = 8.1, 10.5 Hz, 1 H, 3-H), 2.28 (dd, 1 H, *J* = 7.6.10.5 Hz, 3-H), 2.85 (dd, *J* = 3.8, 10.5 Hz, 1 H, C*H*$_2$Cl), 2.99 (dd, *J* = 9.5, 10.5 Hz, 1 H, C*H*$_2$Cl), 3.43 (m, 1 H, 2-H), 3.51 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 3.83 (d, 1 H, $J_{AB}$ = 12.9 Hz, Bn), 7.11−7.44 (m,10 H). $^{13}$C NMR: δ = 20.1 (Me), 38.1 (*C*-3), 47.3 (*C*$H_2$Cl), 54.0 (*C*$H_2$Ph), 60.8 (*C*-2), 62.3 (*C*-4), 123.6, 125.5, 126.4, 127.0, 127.3, 128.1, 138.5, 148.3. $C_{18}H_{20}ClN$: calcd. C 75.64, H 7.05, N 4.90; found C 75.31, H 6.96, N 5.11.

**1-Benzyl-2-(chloromethyl)-4,4-diethylazetidine (14i):** Oil. 0.160 g, 65% yield. $^1$H NMR: δ = 0.88 (t, *J* = 7.3 Hz, 3 H, Me), 0.89 (t, *J* = 7.3 Hz, 3 H, Me), 1.25−1.90 (m, 5 H, 3-H and $CH_2$Me), 2.01 (dd, *J* = 7.8, 10.9 Hz, 1 H, 3-H), 2.97 (dd, 1 H, *J* =.4.3, 10.3 Hz, C*H*$_2$Cl), 3.10 (t, *J* = 10.3 Hz, 1 H, C*H*$_2$Cl), 3.33 (m, 1 H, 2-H), 3.51 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 3.84 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 7.15−7.35 (m, 5 H, Ph). $^{13}$C NMR: δ = 8.3 (Me), 9.0 (Me), 25.2 (*C*$H_2$Me), 31.5 (*C*$H_2$Me), 32.3, 49.0 (*C*$H_2$Cl), 54.8 (*C*$H_2$Ph), 61.9 (*C*-2), 65.8 (*C*-4), 128.1, 128.5, 128.7, 129.2, 129.6, 131.9. $C_{15}H_{22}ClN$: calcd. C 71.55, H 8.81, N 5.56; found C 71.88, H 8.97, N 5.31.

**1-Benzyl-2-(chloromethyl)-4-ethyl-4-methylazetidine (14j):** Oil. 0.169 g, 71% yield; Stereochemistry not assigned. $^1$H NMR: δ = 0.82 (t, *J* = 7.4 Hz, 3 H, Me), 1.22 (s, 3 H, Me), 1.33 (m, 2 H, C*H*$_2$Me), 1.73 (dd, *J* = 8.0, 11.9 Hz, 1 H, 3-H), 1.85 (dd, *J* = 7.9, 11.9 Hz, 1 H, 3-H), 3.00−3.20 (m, 2 H, C*H*$_2$Cl), 3.33 (m, 1 H, 2-H), 3.49 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 3.73 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 7.20−7.35 (m, 5 H, Ph);. $^{13}$C NMR: δ = 19.0 (Me), 30.1 (Me), 34.2 (*C*-3), 35.3 (*C*$H_2$Me), 48.5 (*C*$H_2$Cl), 54.5 (*C*$H_2$Ph), 61.2 (*C*-2), 62.5 (*C*-4), 126.8, 128.0, 128.7, 138.1. $C_{14}H_{20}ClN$: calcd. C 70.72, H 8.48, N 5.89; found C 70.87, H 8.57, N 5.92.

**Spiro Compound 14k:** Oil. 0.170 g, 65% yield. $^1$H NMR: δ = 0.80−1.70 (m, 10 H, $(CH_2)_5$], 1.87 (dd, *J* = 2.0, 10.6 Hz, 1 H, 3-H), 2.02 (dd, *J* = 7.8, 10.6 Hz, 1 H, 3-H), 3.02−3.12 (m, 2 H, C*H*$_2$Cl), 3.32 (m, 1 H, 4-H), 3.48 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 3.77 (d, 1 H, $J_{AB}$ = 13.2 Hz, Bn), 7.08−7.30 (m, 5 H, Ph). $^{13}$C NMR: δ = 23.4, 23.6, 26.2, 31.1, 34.8 (*C*$H_2$)$_5$, 40.9 (*C*-3), 49.3 (*C*$H_2$Cl), 53.8 (*C*$H_2$Ph), 61.6 (*C*-4), 63.6 (*C*-2), 127.2, 128.5, 129.2, 133.7. $C_{16}H_{22}NCl$: calcd. C 72.84, H 8.41, N 5.31; found C 73.02, H 8.27, N 5.43.

**b) Preparation of the (Bromomethyl)azetidines *cis*-15:** Bromine (240 mg, 1.5 mmol) in heptane (5 mL) was slowly added to a solution of azetidine *cis*-**2** ($R^2$ = H, 1 mmol) at room temp. The dibromoselenurane **13**, formed immediately, was decomposed in the same way as the analogous dichloro adducts **12**. The workup and the chromatographic purification were performed as above. The (bromomethyl)azetidines **15g**, **15h**, and **15k** could not be isolated. In these cases, bromination was carried out in $CH_3CN$ and the ring expansion to bromopyrrolidine **5** was observed directly (see below). The unstable 1-benzyl-2-(bromoethyl)azetidine **9a** was not isolated with analytical purity.

**1-Benzyl-2-(bromomethyl)azetidine (15a):** Unstable oil. $^1$H NMR: δ = 1.90 (m, 1 H, Me), 2.15 (m, 1 H, 3-H), 2.83 (m, 1 H, 4-H), 3.16 (m, 2 H, C*H*$_2$Br), 3.30 (m, 1 H, 4-H), 3.42 (m, 1 H, 2-H), 3.60 (d, 1 H, $J_{AB}$ = 12.6 Hz, Bn), 3.77 (d, 1 H, $J_{AB}$ = 12.6 Hz, Bn), 7.17−7.34 (m, 5 H, Ph). $^{13}$C NMR: δ = 24.2 (*C*-3), 36.9 (*C*$H_2$Br), 50.7 (*C*-4), 63.1 (*C*$H_2$Ph), 66.4 (*C*-2), 127.6, 128.5, 129.6.

***cis*-1-Benzyl-2-(bromomethyl)-4-ethylazetidine (15c):** Oil. 0.180 g, 67% yield. $^1$H NMR: δ = 0.77 (t, *J* = 7.4 Hz, 3 H, Me), 1.25−1.52 (m, 3 H, 3-H and C*H*$_2$Me), 2.26 (m, 1 H, 3-H), 2.90 (m, 1 H, 4-H), 3.03 (m, 2 H, C*H*$_2$Br), 3.16 (m, 1 H, 2-H), 3.61 (d, 1 H, $J_{AB}$ = 12.6 Hz, Bn), 3.75 (d, 1 H, $J_{AB}$ = 12.6 Hz, Bn), 7.18−7.34 (m, 5 H, Ph). $^{13}$C NMR: δ = 9.2 (Me), 29.1 (*C*-3), 29.4 (*C*$H_2$Me), 37.0 (*C*$H_2$Br), 61.9 (*C*$H_2$Ph), 62.4 (*C*-4), 63.3 (*C*-2), 127.1, 128.1, 129.1, 138.5. $C_{13}H_{18}BrN$: calcd. C 58.21, H 6.76, N 5.22; found C 58.38, H 6.78, N 5.30.

***cis*-1-Benzyl-2-(bromomethyl)-4-isopropylazetidine (15d):** Oil. 0.183 g, 65% yield. $^1$H NMR: δ = 0.80 (d, *J* = 9.0 Hz, 3 H, Me), 0.84 (d, *J* = 9.0 Hz, 3 H, Me), 1.46 (m, 1 H, 3-H), 1.61 (m, 1 H, C*H*Me$_2$), 2.23 (m, 1 H, 3-H), 2.73 (m, 1 H, 4-H), 2.85 (m, 1 H, C*H*$_2$Br), 2.97 (m, 1 H, C*H*$_2$Br), 3.12 (m, 1 H, 2-H), 3.49 (d, 1 H, $J_{AB}$ = 12.7 Hz, Bn), 3.87 (d, 1 H, $J_{AB}$ = 12.7 Hz, Bn), 7.19−7.34 (m, 5 H, Ph). $^{13}$C NMR: δ = 17.4 (Me), 18.7 (Me), 27.0 (*C*-3), 33.8 (*C*HMe$_2$), 37.1 (*C*$H_2$Br), 61.9 (*C*-4), 62.5 (*C*$H_2$Ph), 67.4 (*C*-2), 127.1, 128.1, 129.0. $C_{14}H_{20}BrN$: calcd. C 59.57, H 7.14, N 4.96; found C 59.22, H 7.50, N 4.63.

***cis*-1-Benzyl-2-(bromomethyl)-4-*tert*-butylazetidine (15e):** Oil. 0.202 g, 68% yield. $^1$H NMR: δ = 0.86 (s, 9 H, *t*Bu), 1.53 (m, 1 H, 3-H), 2.12 (m, 1 H, 3-H), 2.63−2.86 (m, 2 H, 4-H and C*H*$_2$Br), 2.92 (m, 1 H, C*H*$_2$Br), 3.07 (m, 1 H, 2-H), 3.42 (d, 1 H, $J_{AB}$ = 13.0 Hz, Bn), 3.94 (d, 1 H, $J_{AB}$ = 13.0 Hz, Bn), 7.20−7.34 (m, 5 H, Ph). $^{13}$C NMR: δ = 24.5 (*C*-3), 25.7 (Me), 29.5 (*C*Me$_3$), 37.0 (*C*$H_2$Br), 61.9 (*C*-4), 63.2 (*C*$H_2$Ph), 70.3 (*C*-2), 127.1, 128.1, 128.8. $C_{15}H_{22}BrN$: calcd. C 60.81, H 7.48, N 4.73; found C 60.73, H 7.37, N 4.69.

**1-Benzyl-2-(bromomethyl)-4-methyl-4-phenylazetidine (15h):** Oil. O.230 g, 70% yield. Stereochemistry not assigned. $^1$H NMR: δ = 1.56 (s, 3 H, Me), 1.87 (dd, *J* = 8.3, 10.6 Hz, 1 H, 3-H), 2.29 (dd, *J* = 7.5, 10.6 Hz, 1 H, 3-H), 2.68 (dd, *J* = 3.8, 9.5 Hz, 1 H, C*H*$_2$Br), 2.84 (t, *J* = 9.5 Hz, 1 H, C*H*$_2$Br), 3.43 (m, 1 H, 2-H), 3.51 (d, 1 H, $J_{AB}$ = 12.8 Hz, Bn), 3.85 (d, 1 H, $J_{AB}$ = 12.8 Hz, Bn), 7.10−7.42 (m, 10 H). $^{13}$C NMR: δ = 14.7 (Me), 38.2 (*C*$H_2$Br), 40.8 (*C*-3), 53.9 (*C*$H_2$Ph), 62.2 (*C*-2), 127.3, 127.8, 128.2, 128.5, 129.0.

**Method B. Ring-Expansion of (Halomethyl)azetidines 14 (15) into β-Halopyrrolidines 4 (5):** A solution of (chloromethyl)azetidine **14** (1 mmol) in $CH_3CN$ (10 mL) was heated at reflux for 2 h. The solvent was eliminated under reduced pressure and the oily chloropyrrolidine **4** was purified by flash chromatography on silica gel (elution: 30:70 hexane/$CHCl_3$ mixture). The *cis*-bromopyrrolidines **5c**, **5d**, and **5e** were prepared by the same procedure. The formation and the decomposition of the unstable 2,2-disubstituted 4-(bromomethyl)azetidines **15g**, **15h**, and **15k** were achieved directly in $CH_3CN$. The reaction mixture was hydrolysed with aq. $Na_2CO_3$ prior to chromatographic purification.

***cis*-1-Benzyl-4-chloro-2-ethylpyrrolidine (4c):** Oil. 0.156 g, 70% yield. $^1$H NMR: δ = 0.86 (t, *J* = 7.4 Hz, 3 H, Me), 1.46 (m, 1 H, C*H*$_2$Me), 1.72 (m, 1 H, C*H*$_2$Me), 1.84 (m, 1 H, 3-H), 2.42−2.47(m, 2 H, 2-H and 3-H), 2.53 (m, 1 H, 5-H), 3.03 (d, *J* = 11.0 Hz, 1 H, 5-H), 3.17 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 4.01 (d, 1 H, $J_{AB}$ = 13.4 Hz, Bn), 4.23 (m, 1 H, 4-H), 7.13−7.30 (m, 5 H, Ph). $^{13}$C NMR: δ = 9.0 (Me), 24.9 (*C*$H_2$Me), 40.7 (*C*-3), 54.3 (*C*-4), 56.2 (*C*$H_2$Ph), 61.9 (*C*-5), 63.8 (*C*-2), 125.9, 127.2, 127.6, 128.3. $C_{13}H_{18}ClN$: calcd. C 69.78, H 8.11, N 6.26; found C 69.47, H 8.25, N 6.43.

***cis*-1-Benzyl-4-chloro-2-isopropylpyrrolidine (4d):** Oil. 0.130 g, 55% yield. $^1$H NMR: δ = 0.90 (d, *J* = 6.9 Hz, 3 H, Me), 0.99 (d, *J* = 6.9 Hz, 3 H, Me), 1.91 (m, 1 H, 3-H), 2.02 (m, 1 H, C*H*Me$_2$), 2.32 (m, 1 H, 3-H), 2.45 (m, 1 H, 2-H), 2.56 (dd, *J* = 5.3, 10.6 Hz, 1 H,

5-H), 3.07 (d, $J$ = 10.6 Hz, 1 H, 5-H), 3.16 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.05 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.27 (m, 1 H, 4-H), 7.20−7.36 (m, 5 H, Ph). $^{13}$C NMR: δ = 15.5 (Me), 20.0 (Me), 28.1 (*C*HMe$_2$), 36.7 (*C*-3), 55.4 (*C*-4), 57.5 (*C*H$_2$Ph), 62.9 (*C*-5), 68.8 (*C*-2), 126.8, 128.2, 128.4, 129.1, 131.4. $C_{14}H_{20}ClN$: calcd. C 70.72, H 8.48, N 5.89; found C 70.89, H 8.38, N 6.05.

***cis*-1-Benzyl-2-*tert*-butyl-4-chloropyrrolidine (4e):** Oil. 0.168 g, 68% yield.$^1$H NMR: δ = 0.87 (s, 9 H, *t*Bu), 2.03−2.12 (m, 2 H, 3-H), 2.68 (dd, $J$ = 4.0, 12.0 Hz, 1 H, 5-H), 2.95 (m, 1 H, 2-H), 3.13 (dd, $J$ = 4.2, 12.0 Hz, 1 H, 5-H), 3.89 (d, 1 H, $J_{AB}$ = 14.2 Hz, Bn), 4.05 (d, 1 H, $J_{AB}$ = 14.2 Hz, Bn), 4.27 (m, 1 H, 4-H), 7.20−7.40 (m, 5 H, Ph). $^{13}$C NMR: δ = 25.7 (Me), 37.5 (*C*-3), 54.9 (*C*-4), 61.8 (*C*H$_2$Ph), 62.8 (*C*-5), 71.5 (*C*-2), 126.7, 127.2, 128.2, 130.5. $C_{15}H_{22}ClN$: calcd. C 71.55, H 8.80, N 5.56; found C 71.26, H 8.68, N 5.77.

***cis*-1-Benzyl-4-bromo-2-ethylpyrrolidine (5c):** Oil. 0.154 g, 58% yield. $^1$H NMR: δ = 0.92 (t, $J$ = 7.4 Hz, 3 H, Me), 1.40−1.62 (m, 1 H, C*H*$_2$Me), 1.68−1.87 (m, 1 H, C*H*$_2$Me), 2.04 (ddd, 1 H, $J$ = 3.2, 7.7, 10.5 Hz, 3-H), 2.46 (ddd, $J$ = 3.2, 7.7, 7.9 Hz, 1 H, 3-H), 2.55−2.70 (m, 2 H, 2-H and 5-H), 3.18 (dd, $J$ = 2.5, 11.7 Hz, 1 H, 5-H), 3.24 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.05 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.30 (m, 1 H, 4-H), 7.16−7.38 (m, 5 H, Ph). $^{13}$C NMR: δ = 10.1 (Me), 26.0 (*C*H$_2$Me), 42.2 (*C*-3), 45.0 (*C*-4), 57.1 (*C*H$_2$Ph), 63.3 (*C*-5), 65.0 (*C*-2), 126.8, 128.1, 128.4, 138.8. $C_{13}H_{18}BrN$: C,58.21, H 6.76, N 5.22; found C 57.87, H 6.61, N 5.35.

***cis*-1-Benzyl-4-bromo-2-isopropylpyrrolidine (5d):** Oil. 0.155 g, 55% yield. $^1$H NMR: δ = 0.91 (d, $J$ = 6.9 Hz, 3 H, Me), 1.00 (d, $J$ = 6.9 Hz, 3 H, Me), 1.98−2.10 (m, 2 H, C*H*Me$_2$ and 3-H), 2.43 (m, 1 H, 3-H), 2.51 (m, 1 H, 2-H), 2.65 (dd, $J$ = 5.8, 11.6 Hz, 1 H, 5-H), 3.17 (dd, $J$ = 2.8, 11.6 Hz, 1 H, 5-H), 3.19 (d, 1 H, $J_{AB}$ = 13.7 Hz, Bn), 4.04 (d, 1 H, $J_{AB}$ = 13.7 Hz, Bn), 4.30 (m, 1 H, 4-H), 7.20−7.38 (m, 5 H, Ph). $^{13}$C NMR: δ = 15.7 (Me), 20.0 (Me), 28.3 (*C*HMe$_2$), 37.4 (*C*-3), 45.2 (*C*-4), 57.6 (*C*H$_2$Ph), 63.3 (*C*-5), 69.0 (*C*-2), 126.7, 128.2, 128.8, 138.4. $C_{14}H_{20}BrN$: C,59.57, H 7.14, N 4.96; found C59.19, H 6.96, N 5.12.

***cis*-1-Benzyl-4-bromo-2-*tert*-butylpyrrolidine (5e):** Oil. 0.176 g, 60% yield. $^1$H NMR: δ = 0.95 (s, 9 H, *t*Bu), 1.82 (m, 1 H, 3-H), 2.46 (m, 1 H, 3-H), 2.68−2.85 (m, 2 H, 2-H and 5-H), 2.92 (t, $J$ = 9.2 Hz, 1 H, 5-H), 3.62 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 3.87 (d, 1 H, $J_{AB}$ = 13.6 Hz, Bn), 4.10 (m, 1 H, 4-H), 7.16−7.36 (m, 5 H, Ph). $^{13}$C NMR: δ = 26.8 (Me), 40.5 (*C*-3), 45.1 (*C*-4), 58.6 (*C*H$_2$Ph), 63.4 (*C*-5), 69.9 (*C*-2), 126.6, 128.3, 128.5, 138.1. $C_{15}H_{22}BrN$: calcd. C 60.81, H 7.48; N,4.73; found C 60.97, H 7.38, N 5.03.

**C) Method C. Halogenation of the (Phenylselanyl)pyrrolidines *cis*-3. a) Preparation of the Chloropyrrolidines *trans*-4:** A solution of $SO_2Cl_2$ (200 mg,1.5 mmol) in $CH_2Cl_2$ (3 mL) was slowly added at room temp., whilst stirring, to the (phenylselanyl)pyrrolidine *cis*-**3** (1 mmol), dissolved in the same solvent (3 mL). The dichloro adduct **16** progressively disappeared. The reaction was stirred for 0.5 h, treated with aqueous sodium carbonate and diluted with water. The aqueous phase was extracted with $CH_2Cl_2$. The organic layers were dried and concentrated. The oily residue was chromatographed on silica gel. Diphenyldiselenide was removed with hexane, and elution with 40:60 $CH_2Cl_2$/hexane afforded pure chloropyrrolidine *trans*-**4**.

The *trans* isomers of **4b**, **4c**, **4d**, **4e**, and **4f** were prepared in this way. The yields are given in the Table 1, method C). The unstable pyrrolidine **4a**[20] could not be isolated in pure form.

**b) Preparation of the Bromopyrrolidines *trans*-5:** Bromine (240 mg, 1.5 mmol) in $CH_2Cl_2$ (3 mL) was added dropwise at room temperature to a stirred solution of (phenylselanyl)pyrrolidine *cis*-**3** (1 mmol) in the same solvent (3 mL). The dibromo adduct **17**, formed immediately, then disappeared. The reaction mixture was stirred for 20 min and was then treated as above. Chromatographic purification allowed the isolation of **5b**, **5c**, **5d**, **5e**, and **5f** (*trans* isomers) (yields are given in the Table 1, method C). The known bromopyrrolidine **5a**[18,19]was not obtained in pure form.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