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Selenium-promoted synthesis of enantiopure octahydroindolizines, hexahydro-1*H*-pyrrolizines and hexahydro-3*H*-pyrrolizin-3-ones

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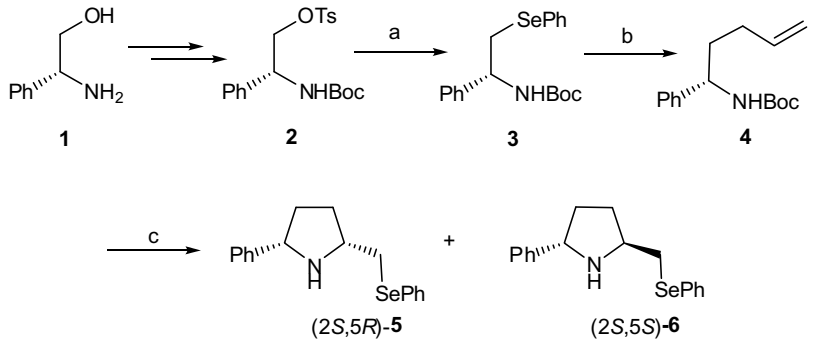
ABSTRACT

Enantiomerically pure disubstituted pyrrolidines, recently synthesized from commercially available enantiomerically pure β-aminoalcohol, were used as starting materials to synthesize enantiomerically pure hexahydro-1*H*-pyrrolizines and octahydroindolizine through a cyclization reaction promoted by *N*-(phenylseleno)phthalimide. Similarly, starting from enantiopure 5-(hydroxymethyl)pyrrolidin-2-ones, enantiopure hexahydro-3*H*-pyrrolizin-3-ones were obtained.

1. Introduction

Pyrrolidine, piperidine heterocycles, and their fused analogs are ubiquitous in nature, and display a wide range of biological activities.[1] In particular, hexahydro-1*H*-pyrrolizines and octahydroindolizines are structural units present in compounds, which have several applications in biological and therapeutic fields.[2] Several polyhydroxylated octahydroindolizines and hexahydro-1*H*-pyrrolizines have shown inhibitory action toward various glycosidate enzymes.[3] Moreover, the hexahydro-1*H*-pyrrolizines together with octahydroindolizines represent a new class of non-opiate antinociceptive agents.[4] Due to their importance, some synthetic approaches for the preparation of these bicyclic nitrogen heterocycles have been reported in the literature.[3,5,6] On the basis of our previous experiences, we thought that a very convenient alternative procedure could involve an asymmetric cyclization reaction promoted by selenium reagents.[7]

Whereas considerable attention has been devoted to cyclization reactions leading to the pyrrolidine ring,[8,9] only sporadic examples have been described for bicyclic nitrogen heterocycles.[10] We have recently described the synthesis of enantiomerically pure substituted pyrrolidines starting from commercially available aminoalcohols[11] and using simple organoselenium reagent promoted conversions.[12] As indicated in Scheme 1, the (*R*)-2-phenylglycinol **1**, after double protection, was converted into the β-amino selenide **3** by displacing the tosyl group with phenyl selenolate anion. The phenylseleno group was then substituted by an allyl group. The reaction of this allylic derivative with an electrophilic phenylselenium reagent afforded the two diastereoisomeric 2-phenyl-5-[(phenylseleno)methyl] pyrrolidines **5** and **6**, as the result of a



Scheme 1. Reagents and conditions: (a) $(PhSe)_2$, $NaBH_4$, DMF, 40 °C; (b) $SnBu_3$, AIBN, C_6H_6, 80 °C; (c) N-PSP, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt.

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5-*exo-trig* cyclization. These two products were easily separated by column chromatography. The presence of the organoselenium function in the cyclization products **5** and **6** allowed the introduction of several other groups to be easily effected.[11,13]

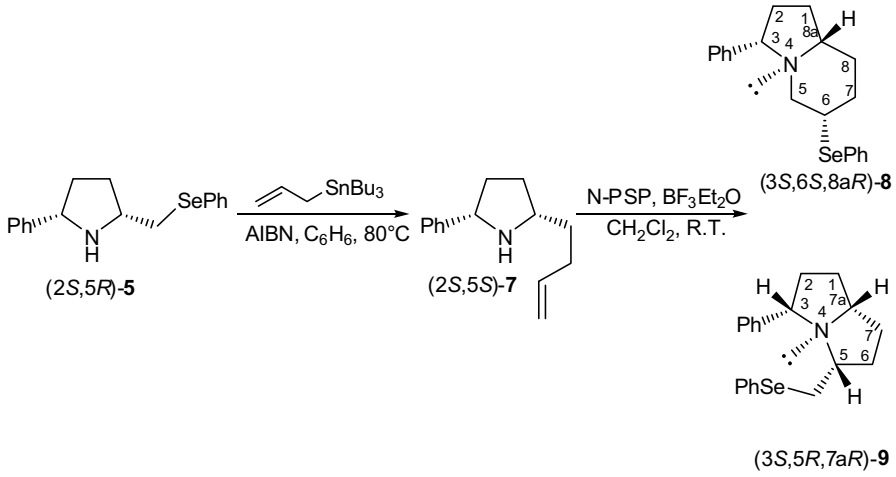
Herein, we report that the radical substitution of the phenylseleno moiety by an allyl group gives rise to allyl derivatives, which can be used to effect cyclization reactions to afford enantiopure hexahydro-1*H*-pyrrolizines and octahydroindolizines.

2. Results and discussion

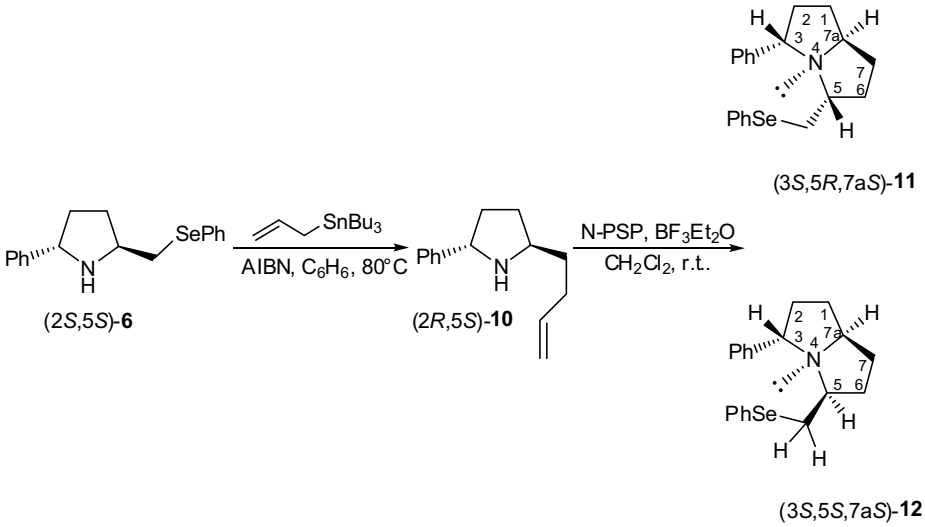
The radical substitution of the phenylseleno group of compounds **5** with an allyl group was affected by treatment with allyltributyltin and AIBN in refluxing benzene. The resulting allylated product **7** contains a double bond and an internal nitrogen nucleophile, and it can be subjected to electrophilic cyclization promoted by *N*-(phenylseleno)phthalimide in the presence of BF_3. As indicated in Scheme 2, this reaction afforded the 3-phenyl-6-[(phenylseleno)methyl]octahydroindolizine **8** (7%) and 3-phenyl-5-[(phenylseleno)methyl]hexahydro-1*H*-pyrrolizine **9** (40%). These two compounds were separated by column chromatography.

Structural attributions were made on the basis of the chemical shift values of protons at the 7a and 8a positions[14] and on the basis of the results of NOESY experiments. The chemical shift values of the bridgehead proton in octahydroindolizine **8** and hexahydro-1*H*-pyrrolizine **9** are 2.20 ppm and 2.75 ppm, respectively, implying that these protons are *trans* to the nitrogen lone pair.[14] Moreover, in the NOESY experiment of compound **9** a strong dipolar interaction between the proton at the 3-position and the protons at the 5 and 7a positions was observed, indicating that the phenyl group and the CH_2SePh are in the opposite side of the bridgehead proton 7a. The stereochemistry of the SePh substituent in the octahydroindolizine **8** was tentatively assigned by the values of the vicinal coupling constants of the proton H_6 with the protons at the 5 and 7 positions assuming a chair conformation of the six-membered ring. All these coupling constants are small. The absence of large axial–axial constants can be taken as an indication that the SePh group occupies an axial position.

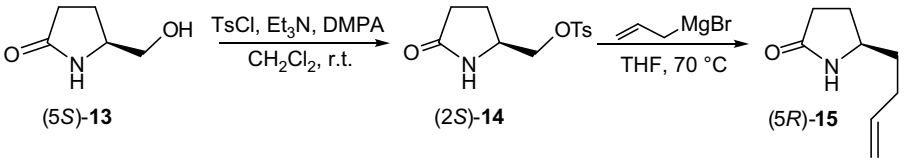
Starting from the allylated product **10,** obtained from the pyrrolidine **6**, the *5-exo trig* selenocyclization reaction afforded the two enantiopure diastereoisomers, hexahydro-1*H*-pyrrolizines **11** (25%) and **12** (23%), which were separated by column chromatography (Scheme 3).



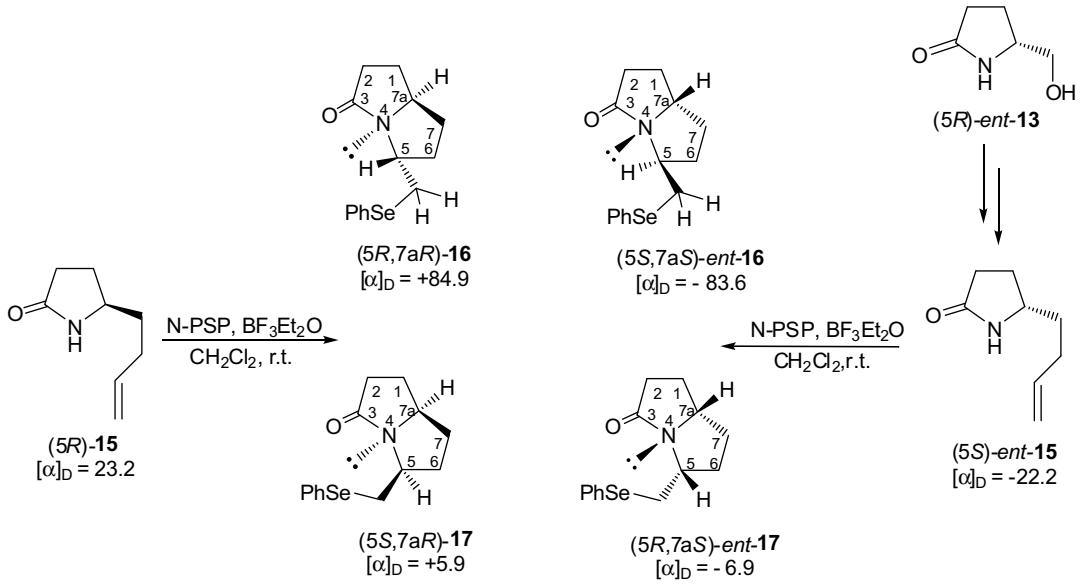
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

The chemical shift values of the bridgehead proton H_{7a} in the hexahydro-1*H*-pyrrolizines **11** and **12** are 3.86 ppm and 3.80 ppm, respectively. These values are characteristic for *cis*-fused hexahydro-1*H*-pyrrolizines in which protons H_{7a} are *cis* to the nitrogen lone pair.[14] Moreover, the NOESY experiment of compound **11** showed a strong dipolar interaction between the proton at the 3-position and the proton at the 5-position. In compound **12**, the NOE effect was observed between the proton in the 3-position and the two protons of CH_2SePh group. Further indications for the proposed structures came from the ^{13}C NMR spectra. The chemical shift of the carbon C_{7a} in compound **9** appears at 72.2 ppm. Similar values are reported for *trans*-fused hexahydro-1*H*-pyrrolizines. In compounds **11** and **12**, the C_{7a} signals appear at 66.6 ppm and 66.9 ppm, respectively, which is consistent with chemical shifts reported for *cis*-fused hexahydro-1*H*-pyrrolizines.[14a]

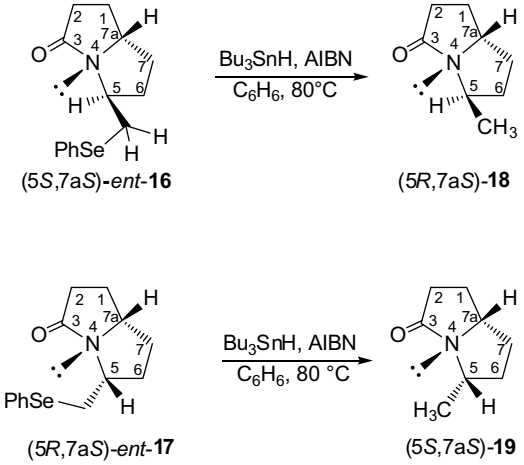
Similar cyclization reactions were then carried out on the allyl derivatives of pyrrolidin-2-ones. The starting product (5*R*)-5-but-3-en-1-ylpyrrolidin-2-one[15] **15** was easily obtained in very good yields from the commercially available (5*S*)-5-(hydroxymethyl)pyrrolidin-2-one, **13** (ee >99%) (Scheme 4).

The 5-*exo*-*trig* selenocyclization reaction of **15** gave rise to a mixture of the two diastereoisomeric 5-[(phenylseleno)methyl]-hexahydro-3*H*-pyrrolizin-3-ones **16** (22%) and **17** (54%) (Scheme 5). The two products were obtained in enantiomerically pure form by medium pressure liquid chromatography.

The same synthetic sequence was then repeated starting from (5*R*)-5-(hydroxymethyl)pyrrolidin-2-one, *ent*-**13**, to give the bicyclic products *ent*-**16** (25%) and *ent*-**17** (45%) (Scheme 5).

These cyclization products were formed in higher yields in comparison to **9**, **11**, and **12**. The better results observed with **13** and *ent*-**13** can be probably attributed to a decrease of the nucleophilic power of the nitrogen atom, as previously observed by us[11] and by other research groups.[8d] Due to the presence of the carbonyl and phenylselenium groups, these products can be employed for further interesting transformations.[10a]

The enantiomeric purities of the hexahydro-3*H*-pirrolizin-3-ones **16,** *ent*-**16, 17** and *ent*-**17** were confirmed by HPLC analysis on chiral column Chiralpak AD-H. The *cis* fusion of these bicyclic derivatives was established on the basis of the chemical shift values of proton and carbon-13 at the 7a positions[14a] (3.96 ppm and 62.1 ppm for compound **16** and *ent*-**16**, and 3.91 ppm and 64.4 ppm for compound **17** and *ent*-**17**). Moreover, in the case of



Scheme 6.

compound **16** a NOESY experiment revealed a strong dipolar interaction between the proton in 7a position and the two protons of the CH_2SePh group.

The proposed structures were further confirmed by converting hexahydro-3*H*-pyrrolizin-3-ones *ent*-**16** and *ent*-**17** into the deselenenylated products as previously described in the literature.[16] For this purpose, *ent*-**16** and *ent*-**17** were treated with tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene to afford **18** (65%) and **19** (70%) (Scheme 6).

In the ^{1}H NMR, the protons H_5 and H_{7a} of compound **18** appeared as a multiplet at 4.00–3.85 ppm [lit.[16] δ 4.16–3.55 ppm]. On the other hand, in compound **19**, these signals were observed at 3.70 and 3.90 ppm, respectively [lit.[16] δ 3.55 and 3.95 ppm].

3. Conclusions

The present method describes a simple synthetic method for obtaining enantiopure hexahydro-1*H*-pyrrolizines and octahydroindolizines starting from commercially available compounds. These products can be easily obtained by cyclization reactions promoted by an organoselenium reagent. Similar bicyclic nitrogen containing heterocycles are widespread in Nature and capable of effecting a large number of biological processes.[1–4]

4. Experimental

All new compounds were characterized by MS, ^{1}H, and ^{13}CNMR spectra. GC analyses and MS spectra were carried out with an HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass Selective Detector; for the ions containing selenium, only the peaks arising from the selenium-80 isotope are given. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.62 MHz, respectively, on a Bruker DRX 400 instrument; $CDCl_3$ was used as the solvent, and TMS as the standard. HPLC analyses were performed on an HP 1100 instrument equipped with a chiral column and an UV detector. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

4.1. Starting products

Commercial (*R*)-(+)-2-phenylglycinol (ee 99%), (5*S*)-5-(hydroxymethyl)pyrrolidin-2-one (ee 99%), and (5*R*)-5-(hydroxymethyl) pyrrolidin-2-one (ee 99%) were used without further purification.

4.2. Synthesis of compounds 7 and 10 by radical allylation

To a solution of pyrrolidines **5** and **6** (0.27 g, 0.7 mmol) and a catalytic amount of AIBN in refluxing dry benzene (8 mL) allyltributyltin (1.11 g, 3.5 mmol) was added in 4 h with a syringe pump under nitrogen. The progress of the reactions was monitored by TLC. The solvent was then carefully evaporated under vacuum. The allylated compounds **7** and **10** were isolated in a pure form after column chromatography on deactivated silica gel using a 20:80 mixture of ethyl acetate and light petroleum. Deactivated silica gel was prepared by washing silica gel with a 5% suspension of $NaHCO_3$ in methanol and then by filtering and drying in an oven at 150 °C.[17] Physical and spectral data are reported below.

4.2.1. (2*S*,5*S*)-2-But-3-en-1-yl-5-phenylpyrrolidine, 7

Yield 65%; oil; $[\alpha]_D^{30} = -27.7$ (*c* 2.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.49–7.19 (m, 5H), 5.89 (ddt, 1H, *J* = 6.6, 10.2, 16.8 Hz), 5.08–4.98 (m, 2H), 4.18 (dd, 1H, *J* = 7.7, 7.9 Hz), 3.22 (quint, 1H, *J* = 7.0 Hz), 2.35–2.13 (m, 4H), 2.07–1.95 (m, 1H), 1.82–1.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 144.6, 138.7, 128.3 (two carbons), 126.8, 126.6 (two carbons), 114.4, 62.6, 58.8, 35.8, 33.8, 31.5, 31.4; MS (70 eV, EI): *m*/*z* (rel. int.): 201 (<1%), 198 (100), 144 (29), 104 (20), 91 (14), 77 (8). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.49; H, 9.47; N, 7.02.

4.2.2. (2*R*,5*S*)-2-But-3-en-1-yl-5-phenylpyrrolidine, 10

Yield 68%; oil; $[\alpha]_D^{23} = -48.9$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.49–7.20 (m, 5H), 5.78 (ddt, 1H, *J* = 6.5, 10.0, 16.8 Hz), 5.15–4.90 (m, 2H), 4.30 (dd, 1H, *J* = 6.7, 6.8 Hz), 3.40 (quint, 1H, *J* = 7.2 Hz), 2.40–2.02 (m, 4H), 1.90–1.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 145.5, 138.5, 128.3 (two carbons), 126.6, 126.3 (two carbons), 114.5, 61.5, 58.3, 36.2, 35.0, 32.4, 31.5; MS (70 eV, EI): *m*/*z* (rel. int.): 201 (1), 198 (100), 144 (30), 104 (19), 91 (10), 77 (8). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.51; H, 9.46; N, 6.89.

4.3. Synthesis of 3-phenyl-6-[(phenylseleno)methyl]-octahydroindolizine, 8, 3-phenyl-5-[(phenylseleno)methyl]-hexahydro-1*H*-pyrrolizines, 9, 11, 12, and 5-[(phenylseleno)-methyl]hexahydro-3*H*-pyrrolizin-3-ones, 16, *ent*-16, 17, and *ent*-17 by selenocyclization

To a solution of *N*-(phenylseleno)phthalimide (0.21 g, 0.7 mmol) in dichloromethane (6 mL), compounds **7**, **10** (0.10 g, 0.5 mmol) or compounds **15** and *ent*-**15** (0.07 g, 0.5 mmol) and a catalytic amount of $BF_3{\cdot}Et_2O$ were added at 0 °C. The temperature was allowed to raise to room temperature, and the progress of the reaction was monitored by TLC. The reaction mixture was then poured into a 5% aqueous solution of NaOH and extracted with dichloromethane. The organic layer was dried over sodium sulphate, filtered, and evaporated. 3-Phenyl-5-[(phenylseleno)-methyl]hexahydro-1*H*-pyrrolizines, **9**, **11**, **12**, and 3-phenyl-6-[(phenylseleno)methyl]octahydroindolizine, **8** were separated by flash chromatography using a mixture of diethyl ether and light petroleum (from 5:95 to 20:80). In the case of 5-[(phenylseleno)methyl]hexahydro-3*H*-pyrrolizin-3-ones, **16**, **17**, *ent*-**16** and *ent*-**17**, the reaction mixture was poured into aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. The reaction products were separated by medium pressure chromatography on a silica gel column (Merck, LiChroprep® Si60, 40–63 μm), using a 70:30 mixture of ethyl acetate and light petroleum as an eluent. The separation in a pure form of the two diastereoisomers **16**, **17** and *ent*-**16**, *ent*-**17** was carried out by monitoring the different fractions by GC–MS. Physical and spectral data are reported below. The enantiomeric purity of compounds **16**, *ent*-**16**, **17**, and *ent*-**17** was determined by chiral HPLC (Chiralpack AD-H column (250 × 4.6 mm ID), eluant: hexane/^{i}PrOH 95:5, flow rate 1.0 mL/min, UV detection at 254 nm.

4.3.1. (3*S*,6*S*,8a*R*)-3-Phenyl-6-[(phenylseleno)methyl] octahydroindolizine, 8

Yield 7%; oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.52–7.50 (m, 2H), 7.46–7.43 (m, 2H), 7.40–7.32 (m, 2H), 7.29–7.20 (m, 4H), 3.60–3.55 (m, 1H), 3.22 (dd, 1H, *J* = 7.9, 8.0 Hz), 3.17 (dt, 1H, *J* = 2.1, 11.5 Hz), 2.37 (dd, 1H, *J* = 2.4, 11.5 Hz), 2.21–1.58 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 143.5, 133.4 (two carbons), 131.8, 128.7 (two carbons), 128.2 (two carbons), 127.5 (two carbons), 126.8, 126.6, 69.2, 64.9, 56.5, 43.7, 32.9, 30.6 29.6, 27.9; MS (70 eV, EI): *m*/*z* (rel. int.): 357 (20), 280 (7), 200 (100), 117 (12), 91 (18), 77 (5). Anal. Calcd for $C_{20}H_{23}NSe$: C, 67.41; H, 6.51; N, 3.93. Found: C, 67.33; H, 6.45; N, 3.86.

4.3.2. (3*S*,5*R*,7a*R*)-3-Phenyl-5-[(phenylseleno)methyl] hexahydro-1*H*-pyrrolizine, 9

Yield 40%; oil; $[\alpha]_D^{30} = -11.2$ (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.45–7.41 (m, 2H), 7.40–7.20 (m, 3H), 7.15–7.05 (m, 5H), 3.25 (dd, 1H, *J* = 7.4, 7.6 Hz), 2.82–2.70 (m, 1H), 2.66–2.58 (m, 1H), 2.53 (dq, 1H, *J* = 8.6, 12.5 Hz), 2.51 (dd, 1H, *J* = 3.5, 12.1 Hz), 2.37 (dd, 1H, *J* = 9.5, 12.1 Hz), 2.36 (dq, 1H, *J* = 8.7, 12.5 Hz), 2.15–2.03 (m, 1H), 1.97–1.87 (m, 1H), 1.78–1.65 (m, 2H), 1.66–1.56 (m, 1H), 1.55–1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 145.0, 131.6 (two carbons), 131.0, 128.8 (two carbons), 128.2 (two carbons), 127.8 (two carbons), 127.1, 126.1, 72.2, 64.7, 59.8, 40.4, 36.7, 33.2, 26.3, 25.5; MS (70 eV, EI): *m*/*z* (rel. int.): 357 (1), 186 (100), 91 (8), 77 (3). Anal. Calcd for $C_{20}H_{23}NSe$: C, 67.41; H, 6.51; N, 3.93. Found: C, 67.49; H, 6.58; N, 3.99.

4.3.3. (3*S*,5*R*,7a*S*)-3-Phenyl-5-[(phenylseleno)methyl] hexahydro-1*H*-pyrrolizine, 11

Yield 25%; oil; $[\alpha]_D^{20.6} = -16.7$ (*c* 0.89, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.44–7.38 (m, 2H), 7.36–7.31 (m, 2H), 7.30–7.22 (m, 4H), 7.18–7.13 (m, 2H), 3.86 (quint, 1H, *J* = 7.1 Hz), 3.77 (dd, 1H, *J* = 5.7, 9.5 Hz), 3.15–3.05 (m, 1H), 2.88 (dd, 1H, *J* = 3.7, 12.1 Hz), 2.70 (dd, 1H, *J* = 9.7, 12.1 Hz), 2.27–2.15 (m, 2H), 2.12–1.98 (m, 2H), 1.96–1.82 (m, 1H), 1.80–1.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 145.2, 131.6, 131.5 (two carbons), 128.8 (two carbons), 128.1 (two carbons), 127.1 (two carbons), 126.7, 126.0, 71.0, 66.6, 66.1, 38.0, 34.0, 33.5, 32.6, 30.0; MS (70 eV, EI): *m*/*z* (rel. int.): 357 (2), 200 (8), 186 (100), 143 (19), 128 (17), 115 (10), 91 (24), 77 (7). Anal. Calcd for $C_{20}H_{23}NSe$: C, 67.41; H, 6.51; N, 3.93. Found: C, 67.37; H, 6.44; N, 3.90.

4.3.4. (3*S*,5*S*,7a*S*)-3-Phenyl-5-[(phenylseleno)methyl]-hexahydro-1*H*-pyrrolizine, 12

Yield 23%; oil; $[\alpha]_D^{18.3} = -21.6$ (*c* 0.68, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.65–7.01 (m, 10H), 4.09 (dd, 1H, *J* = 5.6, 9.4 Hz), 3.95–3.75 (m, 1H), 3.49–3.30 (m, 1H), 3.05 (dd, 1H, *J* = 4.1, 12.0 Hz), 2.72 (dd, 1H, *J* = 10.6, 12.0 Hz), 2.42–1.38 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 145.0, 131.9 (two carbons), 131.8, 129.4 (two carbons), 128.7 (two carbons), 127.2 (two carbons), 126.8, 125.9, 66.9, 63.1, 63.0, 39.3, 33.4, 31.8, 31.0, 30.1; MS (70 eV, EI) *m*/*z* (rel. int.): 357 (1), 353 (66), 207 (74), 194 (49) 182 (100), 167 (16), 115 (15), 77 (11). Anal. Calcd for $C_{20}H_{23}NSe$: C, 67.41; H, 6.51; N, 3.93. Found: C, 67.46; H, 6.48; N, 3.87.

4.3.5. (5*R*,7a*R*)-5-[(Phenylseleno)methyl]hexahydro-3*H*-pyrrolizin-3-one, 16

Yield 22%; oil; $[\alpha]_D^{26.9} = 84.9$ (*c* 2.07, $CHCl_3$) HPLC analysis: t_R 29.67 min. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.57–7.53 (m, 2H), 7.29–7.21 (m, 3H), 4.14 (dq, 1H, *J* = 4.0, 7.5 Hz), 4.00–3.93 (m, 1H), 3.26 (dd, 1H, *J* = 3.9, 12.5 Hz), 3.16 (dd, 1H, *J* = 5.2, 12.5 Hz), 2.58–2.48 (m, 1H), 2.39–2.30 (m, 2H), 2.26–2.18 (m, 1H), 2.10–2.04 (m, 1H), 2.00–1.83 (m, 1H), 1.72–1.62 (m, 1H), 1.37–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 174.9, 132.0 (two carbons), 130.0, 129.0 (two carbons), 126.7, 62.1, 53.5, 34.9, 34.1, 33.1, 32.4, 27.1; MS (70 eV, EI) *m*/*z* (rel. int.): 295 (22), 207 (6), 138 (42), 124 (100), 80 (16). Anal. Calcd for $C_{14}H_{17}NOSe$: C, 57.15; H, 5.82; N, 4.76. Found: C, 57.19; H, 5.88; N, 4.87.

4.3.6. (5*S*,7a*S*)-5-[(Phenylseleno)methyl]hexahydro-3*H*-pyrrolizin-3-one, *ent*-16

Yield 25%; oil; $[\alpha]_D^{22.3} = -83.6$ (*c* 1.42, $CHCl_3$). HPLC analysis: t_R 31.71 min. NMR and MS spectra are identical to those of compound **16**. Anal. Calcd for $C_{14}H_{17}NOSe$: C, 57.15; H, 5.82; N, 4.76. Found: C, 57.28; H, 5.90; N, 4.87.

4.3.7. (5*S*,7a*R*)-5-[(Phenylseleno)methyl]hexahydro-3*H*-pyrrolizin-3-one, 17

Yield 54%; oil; $[\alpha]_D^{21.3} = +5.9$ (*c* 1.27, $CHCl_3$). HPLC analysis: t_R 37.44 min. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.58–7.55 (m, 2 H), 7.30–7.21 (m, 3 H), 4.93 (dq, 1 H, *J* = 5.4, 10.4 Hz), 3.92–3.86 (m, 2H), 3.02 (dd, 1H, *J* = 9.5, 12.8 Hz), 2.67 (ddd, 1H, *J* = 7.9, 12.5, 16.5 Hz), 2.44 (dd, 1H, *J* = 8.7, 16.5 Hz), 2.31–2.13 (m, 3H), 1.88 (dt, 1H, *J* = 5.6, 12.1 Hz), 1.74–1.64 (m, 1H), 1.52 (dq, 1H, *J* = 7.2, 12.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 172.2, 131.9 (two carbons), 129.8, 129.5 (two carbons), 126.6, 64.4, 53.1, 37.4, 34.4, 29.4, 28.6, 28.2; MS (70 eV, EI) *m*/*z* (rel. int.): 295 (26), 138 (57), 124 (100), 80 (15). Anal. Calcd for $C_{14}H_{17}NOSe$: C, 57.15; H, 5.82; N, 4.76. Found: C, 57.22; H, 5.89; N, 4.80.

4.3.8. (5*R*,7a*S*)-5-[(Phenylseleno)methyl]hexahydro-3*H*-pyrrolizin-3-one, *ent*-17

Yield 45%; oil; $[\alpha]_D^{22.8} = -6.9$ (*c* 0.68, $CHCl_3$). HPLC analysis: t_R 27.51 min. NMR and MS spectra are identical to those of compound **17**. Anal. Calcd for $C_{14}H_{17}NOSe$: C, 57.15; H, 5.82; N, 4.76. Found: C, 57.20; H, 5.86; N, 4.81.

4.4. Synthesis of 18 and 19 by reductive deselenenylation

To a solution of compounds *ent*-**16** and *ent*-**17** (0.10 g, 0.34 mmol) in dry benzene (3 mL), triphenyltin hydride (0.18 g, 0.51 mmol) and a catalytic amount of AIBN were added, and the mixture was stirred and refluxed for 1 h. The solvent was then removed under reduced pressure. The deselenenylated products were separated by chromatography on a silica gel column using a 70:30 mixture of ethyl acetate and light petroleum as eluent. Physical and spectral data are reported below.

4.4.1. (5*R*,7a*S*)-5-Methyl-hexahydro-3*H*-pyrrolizin-3-one, 18[16]

Yield 65%; oil; $[\alpha]_D^{22.8} = -57.2$ (*c* 2.49, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 4.00–3.85 (m, 2H), 2.75–2.64 (m, 1H), 2.42–2.27 (m, 3H), 2.06–2.00 (m, 1H), 1.68–1.61 (m, 2H), 1.31–1.25 (m, 1H), 1.22 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 174.6, 61.3, 49.5, 36.2, 35.2, 32.9, 26.9, 20.9; MS (70 eV, EI) *m*/*z* (rel. int.): 139 (62), 124 (100), 11 (45), 83 (40), 68 (26), 55 (20). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.11; H, 9.48; N, 10.12.

4.4.2. (5*S*,7a*S*)-5-Methyl-hexahydro-3*H*-pirrolizin-3-one, 19[16]

Yield 70%; oil; $[\alpha]_D^{22.4} = +4.6$ (*c* 1.71, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 3.90 (dquint, 1H, *J* = 5.3, 10.3 Hz), 3.70 (quint, 1H, *J* = 6.8 Hz), 2.68 (ddd, 1H, *J* = 7.8, 12.5, 16.4 Hz), 2.45 (dd, 1H, *J* = 8.8, 16.4 Hz), 2.32–2.22 (m, 1H), 2.18–2.12 (m, 1H), 1.87 (dt, 1H, *J* = 5.8, 11.7 Hz), 1.78 (dd, 1H, *J* = 6.8, 12.8 Hz), 1.70–1.59 (m, 1H), 1.51–1.38 (m, 1H), 1.35 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 172.1, 64.5, 48.8, 37.5, 36.6, 29.3, 28.4, 18.8; MS (70 eV, EI) *m*/*z* (rel. int.): 139 (71), 124 (100), 11 (44), 83 (45), 68 (29), 55 (24). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.08; H, 9.47; N, 10.13.

4.5. Synthesis of the (*R*)- and (*S*)-5-(but-3-en-1-yl)pyrrolidin-2-one, 15 and *ent*-15

The synthesis was carried out according to the literature data[15] and started with the conversion of the commercially available (5*S*)-5-(hydroxymethyl)pyrrolidin-2-one, **13** (ee >99%) to tosylate **14**. Next, the reaction of allylmagnesium bromide with enantiopure (2*S*)-**14**, under refluxing conditions in THF, furnished (5*R*)-**15** after chromatography.[15] The same sequence was carried out starting from the commercially available (5*R*)-5-(hydroxymethyl)pyrrolidin-2-one, *ent*-**13** (ee >99%), converted in enantiopure tosylate

(2*R*)-*ent*-**14**, and finally in (5*S*)-5-but-3-en-1-ylpyrrolidin-2-one *ent*-**15**.

4.5.1. [(2*S*)-5-Oxopyrrolidin-2-yl]methyl 4-methyl benzenesulfonate, 14[15]

yield 90%; mp 124–127 °C; $[\alpha]_D^{25.3} = 18.5$ (*c* 2.05, $CHCl_3$). ^1H NMR: δ 7.83–7.78 (m, 2 H), 7.43–7.37 (m, 2H), 5.80 (br s, 1H), 4.09 (dd, 1H, *J* = 3.7, 9.5 Hz), 4.01–3.92 (m, 1H), 3.88 (dd, 1H, *J* = 7.4, 9.5 Hz), 2.49 (s, 3H), 2.37–2.25 (m, 3H), 1.77–1.74 (m, 1H). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.58; H, 5.69; N, 5.25.

4.5.2. [(2*R*)-5-Oxopyrrolidin-2-yl]methyl 4-methyl benzenesulfonate, *ent*-14

yield 95%; mp 119–123 °C; $[\alpha]_D^{24.3} = -19.2$ (*c* 1.98, $CHCl_3$). ^1H NMR data are identical to these of compound **14**. Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.56; H, 5.63; N, 5.28.

4.5.3. (5*R*)-5-But-3-en-1-ylpyrrolidin-2-one, 15[15]

Yield 70%; oil; $[\alpha]_D^{22.9} = +23.2$ (*c* 1.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.12 (br s, 1H), 5.77 (ddt, 1H, *J* = 6.6, 10.1, 16.9 Hz), 5.01–4.78 (m, 2H), 3.62 (quint, 1H, *J* = 6.7 Hz), 2.30–2.24 (m, 2H), 2.09 (q, 2H, *J* = 6.6 Hz), 1.75–1.49 (m, 4H). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.06; H, 9.53; N, 10.18.

4.5.4. (5*S*)-5-But-3-en-1-ylpyrrolidin-2-one, *ent*-15

Yield 68%; oil; $[\alpha]_D^{21.5} = -22.2$ (*c* 2.22, $CHCl_3$). ^1H NMR data are identical to those of compound **15**. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.09; H, 9.43; N, 10.08.

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