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Synthesis of chiral 1,5-disubstituted pyrrolidinones via electrophile-induced cyclization of 2-(3-butenyl)oxazolines derived from (1*R*,2*S*)- and (1*S*,2*R*)-norephedrine

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Abstract—Starting from (1*R*,2*S*)- and (1*S*,2*R*)-norephedrine, enantiomers of the corresponding 2-(3-butenyl)oxazolines were prepared in a two-step process. The cyclization of the intermediate alkenylamides with phenylselenyl bromide afforded cyclic imidates instead of the expected pyrrolidinones. The electrophile-induced cyclizations of 2-alkenyloxazolines with bromine or iodine produced diastereomeric mixtures of chiral 1,5-disubstituted pyrrolidinones. The ring closure of the all-*cis* (1*R*,2*S*,5*R*)-diastereomer **7** with NaH resulted in the tetrahydropyrrolo[2,1-*b*]oxazol-5-one derivative **18**, which was alternatively prepared by the cyclocondensation of (1*R*,2*S*)-norephedrine with levulinic acid.

1. Introduction

The electrophile-induced cyclization of alkenylamides and 2-alkenyloxazolidines is of great interest since it allows access to functionalized lactones or lactams, which are known to be interesting synthons for natural product syntheses.[1–7] The cyclization process can proceed in different ways. Depending on the experimental conditions, lactones or lactams can be formed with electrophilic reagents, the most frequently used being iodine, bromine and arylselenyl bromide derivatives. During the ring-closing process, an onium moiety is formed through electrophilic attack on the double bond, after which the nitrogen or oxygen atom of the amide can induce cyclization. After N-attack, lactams are produced, while O-attack furnishes imidates, the hydrolysis of which leads to the corresponding lactones. γ-Lactams, for example, chiral 2-methyl-4-pyrrolidinones, are appropriate reagents for the determination of the enantiomeric composition of alcohols,[8] or they can serve as precursors for the total synthesis of natural products or pharmacologically active compounds.[9–11] γ-Lactams allow further transformations into various bicyclic lactams possessing the nitrogen atom at the bridgehead. Similar bicyclic compounds could also be synthesized with high chemo- and diastereoselectivity by the condensation of 1,2-aminoalcohols with γ-oxoacids.[12–14]

(1*R*,2*S*)- and (1*S*,2*R*)-norephedrine have found widespread use for asymmetric synthesis as catalysts or starting materials. For example, their derivatives are excellent catalysts for the enantioselective Mukaiyama–Michael and Diels–Alder reactions.[15] *N*-Benzyl-substituted norephedrine derivatives are efficient ligands for chiral Ru(III)-catalysed hydrogenation transfer to functionalized ketones.[16] This protocol can also be utilized for the asymmetric reduction of ketimines and *N*-alkylketimines.[17] N-Alkylation of norephedrines allows the synthesis of substituted piperidine derivatives.[18] Oxazolidines derived from norephedrine can be formed by ring closure, using dehydrating agents under thermal conditions,[19] or condensation reactions with acetals[20] or ketoacids.[21]

One aim of the present research was to investigate the electrophile-induced cyclizations of 2-alkenyl oxazolines

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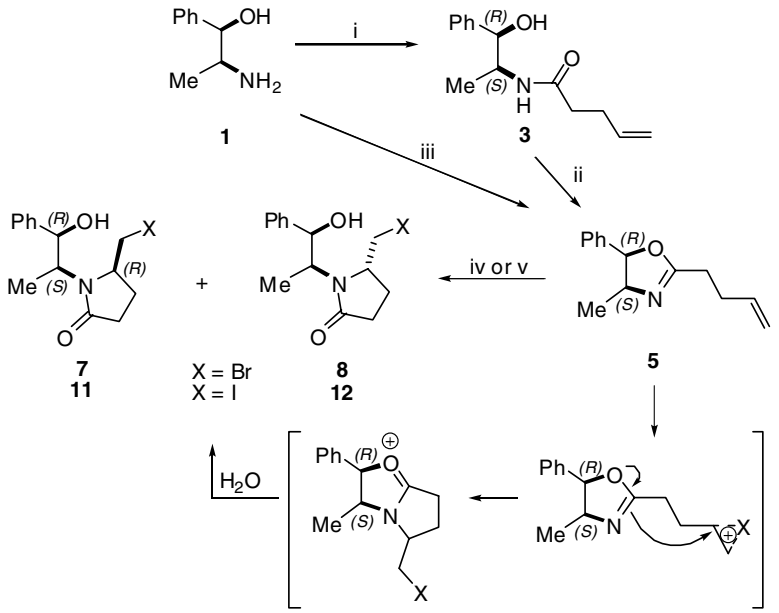
derived from either (+)- or (−)-norephedrines, focusing on the regio- and diastereoselectivity of the cyclization process. A further goal was to study the transformation of the resulting chiral pyrrolidinone derivatives to N-bridged bicyclic heterocycles, for example, pyrrolo[2,1-*c*][1,4]oxazine or pyrrolo[2,1-*b*]oxazole derivatives.

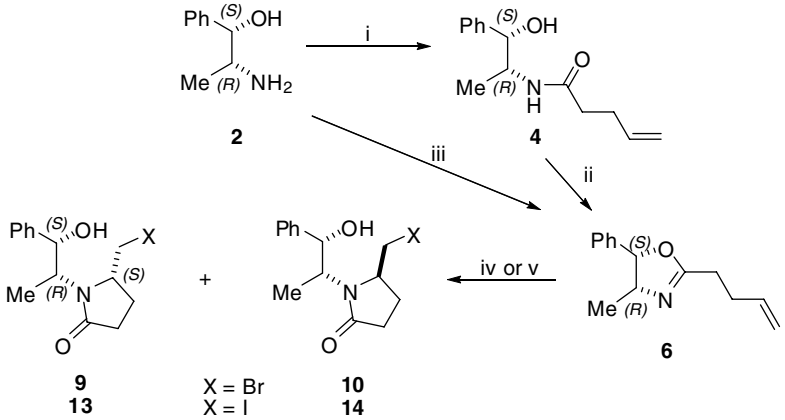
2. Results and discussion

Chiral 3-(3-butenyl)-1,3-oxazolidines **5** and **6** were synthesized by two methods. The starting materials, (1*R*,2*S*)- **1** and (1*S*,2*R*)-norephedrine **2**, were acylated with 4-pentenoyl chloride[22] in dichloromethane in the presence of triethylamine, resulting in amides **3** and **4**. The ring closure of the hydroxyamides **3** and **4** was performed by refluxing in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA), affording oxazoline derivatives **5** and **6** in good yields. In an alternative method, chiral oxazolines **5** and **6** were obtained directly in one step by the reaction of norephedrine and 4-pentenoic acid in toluene at reflux in the presence of a catalytic amount of PTSA. However, the yields of 2-oxazolines **5** and **6** were much lower than in the two-step procedure. Treatment of 2-oxazolines **5** and **6** with bromine in dichloromethane and then with aqueous K_2CO_3, or with iodine in acetonitrile followed by aqueous K_2CO_3, resulted in pyrrolidinones **7**–**14** as a 50:50 (X = Br) or 57:43 (X = I) mixture of diastereomers (Schemes 1 and 2).

Thus, (1*R*,2*S*)-norephedrine **1** and (1*S*,2*R*)-norephedrine **2** were transformed into the corresponding lactams **7**, **8**, **11** and **12** (from **1**) and **9**, **10**, **13** and **14** (from **2**) according to a three-step protocol.



Scheme 1. Reaction conditions: (i) 4-pentenoyl chloride (1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C, 3 h, N_2, 90%; (ii) toluene, PTSA, 48 h reflux, 86%; (iii) 3-butenoic acid (1 equiv), toluene, PTSA, reflux, 3 days, 43%; (iv) Br_2 (1.1 equiv), K_2CO_3, CH_2Cl_2/H_2O, 0 °C, 2.5 h, 56%, diastereomer ratio: 50:50 (**7**:**8**); (v) I_2 (3 equiv), MeCN, −20 °C, 2 h, then $Na_2S_2O_5$, K_2CO_3, 0 °C, 0.5 h, 77%, diastereomer ratio: 57:43 (**11**:**12**).



Scheme 2. Reaction conditions: see in Scheme 1. (i) 57%; (ii) 83%; (iii) 45%; (iv) 53% diastereomer ratio: 50:50 (**9**:**10**); (v) 74%, diastereomer ratio: 57:43 (**13**:**14**).

The electrophile-induced cyclization of 2-(3-butenyl)oxazolines **5** and **6** was highly regioselective but less diastereoselective, and only the formation of the five-membered ring product was observed. Diastereoisomeric γ-lactams **7** and **8** were easily separated by column chromatography, resulting in one isomer in a crystalline form suitable for X-ray diffraction analysis. Accordingly, this X-ray diffraction analysis revealed that γ-lactam **7** was (*R*)-5-bromomethyl-1-[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]pyrrolidin-2-one (Fig. 1). The diastereomeric ratio was determined by ^{1}H NMR, while the relative stereochemistry of product **8** was established by NOESY.

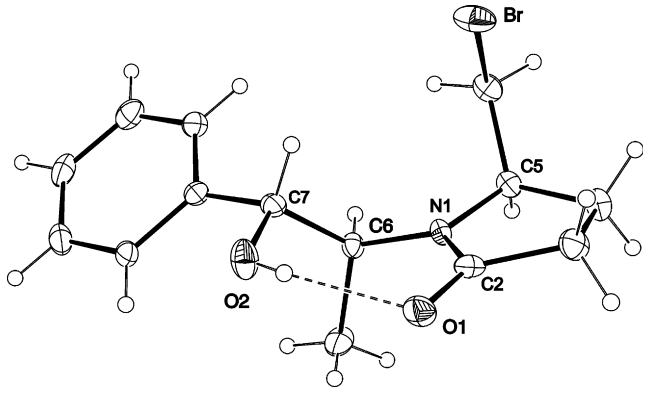


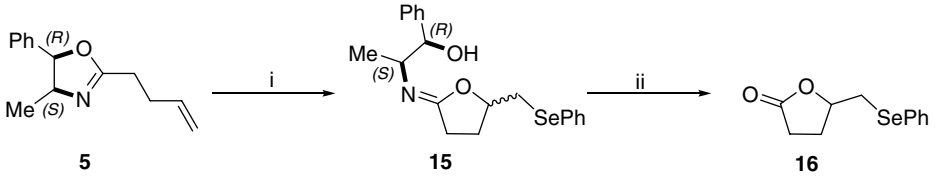
Figure 1. X-ray diffraction structure of pyrrolidinone **7**.

The X-ray crystallographic analysis showed, as depicted in Figure 1, a (1*S*,2*R*,5*R*)-absolute configuration for **7**. The Flack's parameter was 0.002(8) for this configuration. The solid state conformation of **7** is stabilized by an intramolecular hydrogen bond between the OH of the alcohol group and the oxygen of the carbonyl group (OH···O = 2.668(3) Å).

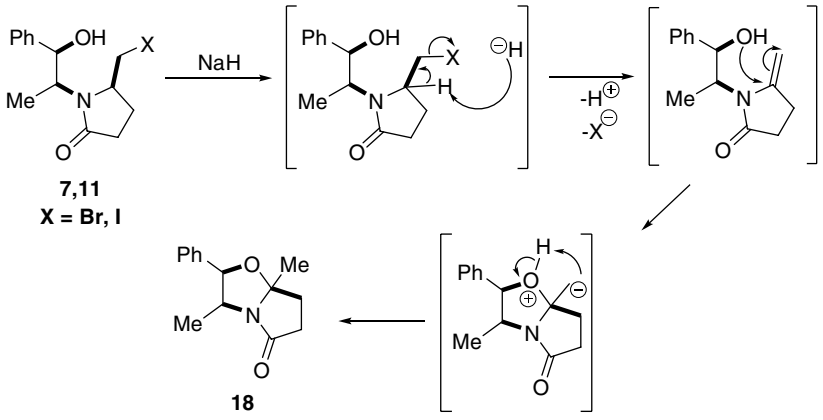
The cyclization of (4*S*,5*R*)-2-oxazoline **5** was also attempted with phenylselenyl bromide in dichloromethane. However, only an inseparable mixture of compounds was obtained. Under similar conditions, intermediate amide **3** underwent an electrophile-induced lactonization instead of the expected lactamization.[1] Iminolactone **15** obtained decomposed during chromatographic purification on silica gel. When **15** was stirred with SiO_2 in dichloromethane, the known[23] racemic lactone **16** was obtained in 95% yield (Scheme 3).

The attempted synthesis of pyrrolo[2,1-*c*][1,4]oxazines **17** (Scheme 5) from γ-lactams **7** and **11** by cyclization with bases, such as NaOMe or NaH, failed. The latter bicyclic morpholines **17** could be suitable precursors of stereodefined 2,3,5-trisubstituted morpholines. Such compounds have received considerable interest in recent years.[24] However, γ-lactams **7** and **11** underwent ring closure to yield pyrrolo[2,1-*b*]oxazol-5-one **18** in a diastereoselective fashion instead of the expected pyrrolo[2,1-*c*][1,4]oxazine **17** (Scheme 4).

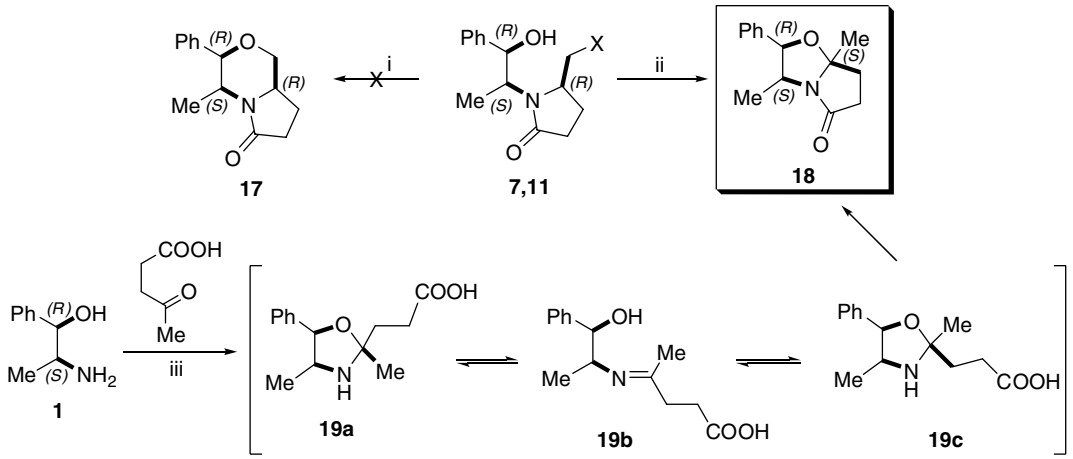
Bicyclic compound **18** was prepared in 80% yield by an alternative synthesis via tandem cyclization of (1*R*,2*S*)-norephedrine with levulinic acid (Scheme 4). This reaction is highly stereoselective as only a single diastereomer was detected in the crude reaction mixture. The stereochemical outcome of this cyclization was also correlated with the findings of Meyers and Burgess.[25–27] The first step in the cyclocondensation process is the reaction of norephedrine



Scheme 3. Reaction conditions: (i) PhSeBr (1 equiv), CH_2Cl_2, 0 °C, 0.5 h, 90%; (ii) SiO_2, CH_2Cl_2, rt, 95%.



Scheme 4. Proposed reaction mechanism for ring closure of diastereomers **7** and **11** to bicyclic compound **18**.



Scheme 5. Reaction conditions: (i) NaOMe or NaH (2–3 equiv), THF, rt to reflux; (ii) NaH (3 equiv), THF, 0 °C to rt, 4 h, 76%; (iii) levulinic acid (1 equiv), toluene, reflux, 32 h, 80%.

with the γ-ketoacid, resulting in a three-component tautomeric mixture.[28,29] From the tautomeric mixture, only intermediate **19c** is suitable as a participant in the second cyclization step to result in (2*R*,3*S*,7a*S*)-3,7a-dimethyl-2-phenylpyrrolo[2,1-*b*]oxazol-5(6*H*)-one **18** (Scheme 5).

3. Conclusion

The electrophile-induced cyclization of chiral 2-(3-butenyl)oxazolines afforded new chiral 1,5-disubstituted pyrrolidinones. The cyclocondensation of 5-halomethyl-γ-lactams resulted in bicyclic lactams with a tetrahydropyrrolo[2,1-*b*]oxazole skeleton, which were alternatively prepared in high yields via the condensation of norephedrine with levulinic acid.

4. Experimental

4.1. General experimental procedures

^{1}H and ^{13}C NMR, DEPT and COSY spectra were recorded on a JEOL JNM-EX270 NMR spectrometer operating at 270 and 67.9 MHz. Optical rotations were measured with an Optical Activity AA-10 polarimeter. IR spectra were measured with a FT-IR spectrometer. Electron impact (EI) mass spectra were obtained with a Varian MAT 112 mass spectrometer, operating at 70 eV. Melting points were measured with a Büchi 535 melting point apparatus, and are uncorrected. Chromatographic separations were performed on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). Toluene was redistilled over metal sodium; acetonitrile and dichloromethane were redistilled over calcium hydride; all other chemicals and solvents were used as supplied. GC measurements were made on a Crompack CP-9002 system, consisting of a Flame Ionization Detector 901A and a Maestro II Chromatography Data System (Chrompack International B.V., Middelburg, The Netherlands). The column used for the direct separation was a Chirasil DEX CB column (2500 × 0.25 mm I.D.) at 160 °C and 80 kPa.

4.2. *N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]-4-pentenamide 3

To a stirred solution of 3.02 g (0.02 mol) of (1*R*,2*S*)-(−)-norephedrine **1** and 2.22 g (0.22 mol) of triethylamine in 100 mL of dry CH_2Cl_2, a solution of 2.38 g (0.02 mol) of 4-pentenoyl chloride in 10 mL of dry CH_2Cl_2 was added dropwise at 0 °C under an N_2 atmosphere. The mixture was stirred for 3 h at 0 °C, and then extracted with a 1 M HCl solution (2 × 50 mL) and water (50 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo, and the crystalline product obtained was recrystallized from EtOAc, resulting in 4.21 g (90%) of pure **3**. Mp: 93–94 °C; $[\alpha]_D^{20} = -111$ (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.99 (d, 3H, $J = 6.9$ Hz, CH_3), 2.23–2.42 (m, 4H, 2 × CH_2), 3.87 (br s, 1H, NH), 4.27–4.34 (m, 1H, C*H*N), 4.80–4.83 (m, 1H, C*H*OH), 4.99–5.09 (m, 2H, CH=*CH*$_2$), 5.73–5.86 (m, 1H, *CH*=CH_2), 7.23–7.37 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 14.2 (CH_3), 29.5 (*CH*$_2$CH=CH_2), 35.6 (NCO*CH*$_2$), 50.9 (CHNH), 76.1 (CHOH), 115.5 (CH=*CH*$_2$), 126.2, 127.3, 128.0 (CH, aromatic), 136.7 (*CH*=CH_2), 140.8 (C_q, aromatic), 173.0 (CO); IR (KBr, cm^{-1}) 3299, 1639, 1550, 702; LRMS (70 eV, *m*/*z*, %) 234 (M+1$^+$, 4), 216 (2), 127 (100). Anal. Calcd for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00. Found: C, 72.18; H, 8.27; N, 5.81.

The (1*R*,2*S*)-enantiomer **4** was prepared as described above; $[\alpha]_D^{20} = +111$ (*c* 1.5, CH_2Cl_2); the spectroscopic data and melting point were similar to those for compound **3**. Anal. Calcd for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00. Found: C, 72.35; H, 8.03; N, 6.17.

4.3. (4*S*,5*R*)-2-(3-Butenyl)-4-methyl-5-phenyl-4,5-dihydro-1,3-oxazole 5

Method A: To a solution of 3.78 g (0.025 mol) of (1*R*,2*S*)-(−)-norephedrine **1** in 80 mL of dry toluene, 2.50 g (0.025 mol) of 4-pentenoic acid and a catalytic amount of

PTSA were added and the mixture was refluxed with a Dean–Stark trap; the water formed being collected for 48 h. The solution was then evaporated to dryness, and the residue was dissolved in EtOAc (200 mL) and washed with 5% $NaHCO_3$ solution (2×50 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo, and the semisolid residue was purified by flash chromatography on silica gel (hexane–EtOAc = 2:1), resulting in 2.3 g of compound **5** (43%, $R_f = 0.45$).

Method B: 1.70 g (7.3 mmol) of amide **3** and a catalytic amount of PTSA were dissolved in 100 mL of dry toluene and the solution was refluxed with a Dean–Stark trap, the water formed was collected for 48 h. The solution was then evaporated to dryness, and the crude product was purified by flash chromatography on silica gel (hexane–EtOAc = 2:1), resulting in 1.35 g of compound **5** (86%, $R_f = 0.45$). $[\alpha]_D^{20} = -170$ (*c* 0.1, MeOH); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.75 (d, 3H, $J = 6.9$ Hz, CH_3), 2.43–2.53 (m, 4H, CH_2CH_2), 4.38–4.44 (m, 1H, CHN), 5.03–5.16 (m, 2H, CH=CH_2), 5.56 (d, 1H, $J = 9.6$ Hz, CHO), 5.85–5.95 (m, 1H, CH=CH_2), 7.18–7.38 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 17.9 (CH_3), 27.6, 30.0 (CH_2CH_2), 64.9 (CHN), 83.8 (CHO), 115.6 (CH=CH_2), 127.8 (CH=CH_2), 126.1, 128.2, 136.9 (CH, aromatic), 137.1 (C_q, aromatic), 166.3 (OC=N); IR (KBr, cm^{-1}) 3066, 2976, 1671, 1455, 1171, 979, 700 ; LRMS (70 eV, *m*/*z*, %) 215 (M^+, 12), 214 (64), 107 (100), 67 (82). Anal. Calcd for $C_{14}H_{17}NO$ (215.30): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.27; H, 8.11; N, 6.41.

The (4*R*,5*S*) enantiomer **6** was prepared as described above; $[\alpha]_D^{20} = +180$ (*c* 0.11, MeOH); the spectroscopic data were similar to those for compound **5**. Anal. Calcd for $C_{14}H_{17}NO$ (215.30): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.32; H, 7.87; N, 6.65.

4.4. (1*S*,2*R*,5*R*)-5-Bromomethyl-1-(2-hydroxy-1-methyl-2-phenylethyl)-2-pyrrolidinone 7; (1*S*,2*R*,5*S*)-5-bromomethyl-1-(2-hydroxy-1-methyl-2-phenylethyl)-2-pyrrolidinone 8

To a stirred solution of 0.45 g (2.1 mmol) of **5** in 20 mL of dry CH_2Cl_2 was added dropwise 0.37 g (2.3 mmol) of Br_2, dissolved in 7 mL of dry CH_2Cl_2, at 0 °C under an N_2 atmosphere. The mixture was stirred for 0.5 h at 0 °C, and 20 mL of 10% K_2CO_3 solution was then added to the solution. After stirring for 2 h at 0 °C the solution was poured into a separatory funnel, the phases were separated and the aqueous phase was extracted once with CH_2Cl_2 (30 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo, and the crude product obtained (diastereomer ratio: 50:50, based on NMR measurement of the crude product) was purified by flash chromatography on silica gel (CH_2Cl_2–EtOAc = 19:1), resulting in 0.18 g (28%, $R_f = 0.32$) of compound **7** and 0.18 g (28%, $R_f = 0.21$) of compound **8**.

Compound **7**: mp: 108–111 °C; $[\alpha]_D^{20} = -42$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.22 (d, 3H, $J = 6.9$ Hz, CH_3), 2.02–2.66 (m, 4H, CH_2CH_2), 3.36 (ddd, 1H, $J = 1.7$, 7.3, 13.3 Hz, CHCH$_2$Br), 3.48–3.59 (m, 2H, CH_2Br), 3.88–3.92 (m, 1H, CHN), 5.21 (br s, 1H, *CH*OH), 5.82 (s, 1H, CH*OH*), 7.24–7.45 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 10.6 (CH_3), 24.8, 31.5, (CH_2CH_2), 36.5 (CH_2Br), 59.9 (*CH*CH$_2$Br), 61.0 (CHN), 76.8 (CHO), 127.0, 128.4, 129.3 (CH, aromatic), 143.4 (C_q, aromatic), 178.4 (C=O); IR (KBr, cm^{-1}) 3198, 1648, 1462, 1291, 753, 704; LRMS (70 eV, *m*/*z*, %) 311 (M^+, 1), 294 (12), 204 (100), 163 (29), 126 (41), 120 (39). Anal. Calcd for $C_{14}H_{18}BrNO_2$ (312.21): C, 53.86; H, 5.81; N, 4.49. Found: C, 54.06; H, 5.87; N, 4.31.

The (1*R*,2*S*,5*S*) enantiomer **9** was prepared and isolated as described above; $[\alpha]_D^{20} = +40$ (*c* 1.0, CH_2Cl_2); the spectroscopic data and melting point were similar to those for compound **7**. Anal. Calcd for $C_{14}H_{18}BrNO_2$ (312.21): C, 53.86; H, 5.81; N, 4.49. Found: C, 53.99; H, 5.65; N, 4.62.

Compound **8**: $[\alpha]_D^{20} = -38$ (*c* 1.05, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.40 (d, 3H, $J = 6.9$ Hz, CH_3), 2.93–2.63 (m, 4H, CH_2CH_2), 3.39–3.53 (m, 4H, $CHCH_2$Br and CHN, overlapping peaks), 4.50 (br s, 1H, CH*OH*), 5.13 (d, 1H, $J = 4.0$ Hz, *CH*OH), 7.23–7.43 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 12.4 (CH_3), 24.4, 31.2 (CH_2CH_2), 36.4 (CH_2Br), 59.2 (*CH*CH$_2$Br), 61.3 (CHN), 76.0 (CHO), 126.7, 128.2, 128.9 (CH, aromatic), 143.0 (C_q, aromatic), 177.4 (C=O); IR (KBr, cm^{-1}) 3333, 3054, 1667, 1266, 738; LRMS (70 eV, *m*/*z*, %) 312 (M^++1, 4), 311 (M^+, 1), 295 (10), 294 (4), 284 (11), 205 (45), 204 (100), 126 (20). Anal. Calcd for $C_{14}H_{18}BrNO_2$ (312.21): C, 53.86; H, 5.81; N, 4.49. Found: C, 53.65; H, 6.09; N, 4.55.

The (1*R*,2*S*,5*R*)-enantiomer **10** was prepared and isolated as described above; $[\alpha]_D^{20} = +39$ (*c* 1.1, CH_2Cl_2); the spectroscopic data were similar to those for compound **8**. Anal. Calcd for $C_{14}H_{18}BrNO_2$ (312.21): C, 53.86; H, 5.81; N, 4.49. Found: C, 53.76; H, 5.93; N, 4.64.

4.5. (1*S*,2*R*,5*R*)-5-Iodomethyl-1-(2-hydroxy-1-methyl-2-phenylethyl)-2-pyrrolidinone 11; (1*S*,2*R*,5*S*)-5-iodomethyl-1-(2-hydroxy-1-methyl-2-phenylethyl)-2-pyrrolidinone 12

To a stirred solution of 0.22 g (1.0 mmol) of oxazoline **5** in 10 mL of dry acetonitrile, 0.75 g (3 mmol) of iodine was added in one portion at −20 °C. After stirring for 2 h at this temperature, the reaction mixture was treated with saturated sodium metabisulfite solution at 0 °C, the solution was basified with 10% K_2CO_3 solution and stirring was continued for a further 30 min at 0 °C. The mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3×80 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo, and the crude product obtained (diastereomer ratio: 57:43, based on NMR measurement of the crude product) was purified by flash chromatography on silica gel (CH_2Cl_2–EtOAc = 19:1), resulting in 0.16 g (44%, $R_f = 0.34$) of compound **11** and 0.12 g (33%, $R_f = 0.22$) of compound **12**.

Compound **11**: mp: 114–116 °C; $[\alpha]_D^{20} = -74$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.19 (d, 3H, $J = 6.9$ Hz, CH_3), 1.83–2.68 (m, 4H, CH_2CH_2), 3.26–3.40 (m, 3H, $CHCH_2$I, overlapping peaks), 3.54–3.62 (m, 1H, CHN), 5.25 (s, 1H, *CH*OH), 5.93 (s, 1H, CH*OH*), 7.23–

7.45 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 9.3 (CH_3), 11.3, 25.3 (CH_2CH_2), 30.2 (CH_2I), 58.7 (*C*HCH$_2$I), 59.6 (CHN), 76.5 (CHO), 125.9, 127.3, 128.2 (CH, aromatic), 142.3 (C_q, aromatic), 177.2 (C=O); IR (KBr, cm^{-1}) 3200, 2936, 1647, 1460, 753, 704; LRMS (70 eV, *m*/*z*, %) 359 (M^+, 1), 341 (1), 252 (100), 126 (20), 112 (10), 97 (8). Anal. Calcd for $C_{14}H_{18}INO_2$ (359.21): C, 46.81; H, 5.05; N, 3.90. Found: C, 46.96; H, 5.01; N, 4.11.

The (1*R*,2*S*,5*S*)-enantiomer **13** was prepared and isolated as described above; $[\alpha]_D^{20} = +73$ (*c* 1.0, CH_2Cl_2); the spectroscopic data and melting point were similar to those for compound **11**. Anal. Calcd for $C_{14}H_{18}INO_2$ (359.21): C, 46.81; H, 5.05; N, 3.90. Found: C, 47.12; H, 5.27; N, 4.02.

Compound **12**: an oil; $[\alpha]_D^{20} = -49$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.42 (d, 3H, $J = 7.3$ Hz, CH_3), 1.76–2.06 (m, 2H, O=CCH$_2$*CH*$_2$), 2.16–2.64 (m, 2H, O=C*CH*$_2$CH$_2$), 3.15–3.44 (m, 4H, CHCH$_2$I and CHN, overlapping peaks), 4.46 (br s, 1H, CH*OH*), 5.12 (d, 1H, $J = 4.3$ Hz, *CH*OH), 7.24–7.41 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 11.8 (CH_2), 13.2 (CH_3), 26.3, 31.3 (CH_2I), 59.5 (*C*HCH$_2$I), 61.8 (CHN), 76.3 (CHO), 127.0, 128.5, 129.2 (CH, aromatic), 143.3 (C_q, aromatic), 177.6 (C=O); IR (KBr, cm^{-1}) 3343, 2938, 1666, 1457, 907, 733, 651; LRMS (70 eV, *m*/*z*, %) 360 (M+H$^+$, 1), 359 (M^+, 1), 342 (5), 341 (12), 252 (100), 126 (22), 112 (6), 97 (10). Anal. Calcd for $C_{14}H_{18}INO_2$ (359.21): C, 46.81; H, 5.05; N, 3.90. Found: C, 46.64; H, 5.17; N, 3.72.

The (1*R*,2*S*,5*R*)-enantiomer **14** was prepared and isolated as described above; $[\alpha]_D^{20} = +48$ (*c* 1.0, CH_2Cl_2); the spectroscopic data and melting point were similar to those for compound **12**. Anal. Calcd for $C_{14}H_{18}INO_2$ (359.21): C, 46.81; H, 5.05; N, 3.90. Found: C, 46.71; H, 4.93; N, 3.65.

4.6. (1*R*,2*S*)-1-Phenyl-2-[((2*Z*)-5-(phenylselenylmethyl)-dihydro-2(3*H*)-furanylidene)amino]-1-propanol 15

To a stirred solution of 0.20 g (0.86 mmol) of carboxamide **3** in 25 mL of dry CH_2Cl_2, 0.20 g (0.86 mmol) of phenylselenyl bromide was added in one portion at 0 °C under N_2. After stirring for 0.5 h at 0 °C, CH_2Cl_2 was added to the solution (20 mL) and the mixture was washed with 10% NaOH solution (15 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo, resulting in a mixture of two diastereomers (oily product, 0.30 g, 90%). The attempted separation of the isomers by chromatography was not successful because of the partial decomposition of the cyclic imidate **15** to lactone **16**.

^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.71 (d, 3H, $J = 7.3$ Hz, CH_3), 1.86–2.10 (m, 2H, CH_2CH_2), 2.50–2.59 (m, 2H), 3.00–3.46 (m, 2H), 3.82–3.86 (m, 1H, *CH*CH$_2$Se), 4.32–4.40 (m, 1H, CHN), 5.52 (dd, 1H, $J = 4.5$, 9.8 Hz, *CH*OH), 7.13–7.53 (m, 10H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 17.57 (CH_3), 24.95, 32.04, 32.10, 35.83 (CH_2), 64.24, 64.31 (N*CH*CH$_2$), 69.60, 69.67 (CH$_3$*CH*N), 83.83 (CHOH), 125.79, 126.72, 127.64, 128.03, 128.90, 132.97 (CH, aromatic), 132.40, 136.50 (C_q, aromatic), 167.37, 167.42 (C=O); IR (NaBr, liquid film, cm^{-1}) 2932, 1667, 1438, 909, 733; LRMS (70 eV, *m*/*z*, %) 388 (M+H$^+$, 2), 389 (M^+, 1), 371 (7), 214 (100), 157 (7), 134 (94). Anal. Calcd for $C_{20}H_{23}NO_2Se$ (388.37): C, 61.85; H, 5.97; N, 3.61. Found: C, 61.72; H, 6.23; N, 3.39.

4.7. 5*R**-5-(Phenylselenylmethyl)dihydro-2(3*H*)-furanone 16[23]

A mixture of 0.79 g (2 mmol) of cyclic imidate **15** and 2.00 g of silica gel in CH_2Cl_2 (30 mL) was stirred for 4 h at room temperature. The silica gel was filtered off and washed with CH_2Cl_2 several times. After evaporation of the solvent, the resulting crude product was identified as lactone **16**. All the analytical and spectroscopic data on compound **16** were similar to those mentioned in the literature.[23]

A pale-yellow crystalline compound: mp: 42–45 °C (lit.[23] mp: 44–46 °C); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.88–2.02 (m, 2H), 2.35–2.64 (m, 3H), 3.01 (dd, 1H, $J = 7.9$, 12.8 Hz), 3.30 (dd, 1H, $J = 4.6$, 12.8 Hz), 4.61–4.71 (m, 1H), 7.28–7.31 (m, 3H), 7.53–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ 27.17, 28.34, 31.50, 78.85, 127.06, 128.82, 128.97, 132.42, 176.28; IR (KBr, cm^{-1}) 2932, 1667, 1438, 909, 733; LRMS (70 eV, *m*/*z*, %) 257 (M+H$^+$, 100), 256 (M^+, 1), 172 (32), 100 (23), 85 (80), 77 (28). Anal. Calcd for $C_{11}H_{12}O_2Se$ (255.17): C, 51.78; H, 4.74. Found: C, 51.59; H, 4.86.

4.8. (2*R*,3*S*,7a*S*)-3,7a-Dimethyl-2-phenylpyrrolo[2,1-*b*]-oxazol-5(6*H*)-one 18

Method A: To a suspension of NaH (53 mg, 1.2 mmol, 60% dispersion in oil) in 5 mL of dry THF, pyrrolidinone derivative **7** (100 mg, 0.32 mmol) was added in small portions. The reaction mixture was allowed to warm up to room temperature and then stirred for 4 h. Afterwards, the excess of NaH was decomposed by means of MeOH (5 mL). The mixture was poured into water (15 mL), the organic phase was separated using $CHCl_3$ (25 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by means of flash chromatography with *n*-hexane–EtOAc (3:2) on Al_2O_3 ($R_f = 0.5$), resulting in the pure compound **18** (60 mg, 76%). Iodomethyl derivative **11** was reacted under the same reaction conditions to furnish bicyclic lactam **18** in 67% yield.

Method B: A mixture of 0.30 g (2 mmol) of (1*R*,2*S*)-norephedrine and 0.23 g (2 mmol) of levulinic acid in 25 mL of toluene was refluxed with a Dean–Stark trap; the water formed was collected for 32 h. The solution was then evaporated in vacuo to dryness, and the residue was purified by flash chromatography on neutral Al_2O_3 (hexane–EtOAc = 2:1), resulting in 0.37 g of compound **18** (80%, $R_f = 0.45$).

A pale-yellow oil; $[\alpha]_D^{20} = -25$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.84 (d, 3H, $J = 7.1$ Hz), 1.69 (s, 3H), 2.16 (dt, 1H, $J = 9.1$, 12.6 Hz), 2.29 (dd, 1H, $J = 8.1$, 12.6 Hz), 2.46 (dd, 1H, $J = 8.3$, 16.3 Hz), 2.67–2.77 (m, 1H), 4.41–4.47 (m, 1H), 4.99 (d, 1H,

$J = 5.45$ Hz, CHN), 7.27–7.38 (m, 5H, CH, aromatic); ^{13}C NMR ($CDCl_3$, 67.9 MHz) 15.9 (CH_3), 28.3 (CH_3), 33.9 (CH_2), 37.8 (CH_2), 55.6 (CH), 82.8 (CH_2), 99.5 (C_q), 126.8, 128.5, 129.0 (CH, aromatic), 137.1 (C_q, aromatic), 178.4 (C=O); IR (KBr, cm^{-1}) 2979, 1709, 1552, 1089, 702; Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.93; H, 7.21; N, 6.19.

4.9. X-ray crystallographic study

Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer using graphite-monochromatized Mo-K_α radiation ($\lambda = 0.71073$ Å). The data were collected by φ and ω rotation scans and processed with the DENZO-SMN v0.93.0 software package.[30] SHELXA absorption correction[31] was also applied for the data.

Crystal data for **7** $C_{14}H_{17}BrN_2$, $M_r = 312.20$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 9.1003(3)$, $b = 9.1587(3)$, $c = 16.6475(5)$ Å, $\alpha, \beta, \gamma = 90°$, $V = 1387.52(8)$ Å^3, $T = 173$ K, $Z = 4$, $\mu(\text{Mo}\,K_\alpha) = 0.282$ mm^{-1}, 2536 unique reflections ($R_{int} = 0.0209$), which were used in calculations. The final $wR(F^2)$ was 0.0544 (all data) and the Flack's parameter was −0.002(8).

The structure was solved by direct methods by use of the SIR97 program[32] and full-matrix, least-squares refinements on F^2 were performed by use of the SHELXL-97 program.[33] The CH hydrogen atoms were included at the fixed distances with the fixed displacement parameters from their host atoms. The OH hydrogen atom was refined isotropically. The figure was drawn with ORTEP-3 for Windows.[34] The deposition number CCDC 615696 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

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