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Conformationally Restricted Analogues of Methionine: Synthesis of Chiral 3-Amino-5-methylthio-2-piperidones

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Abstract — *(αR, 3RS, 5S)*-3-Amino-*N*-(2-hydroxy-1-phenylethyl)-5-methylthio-2-piperidones **1** have been synthesized from enamide **2** by subsequent free radical addition of methanothiol on position 5 and amination of 3-position.
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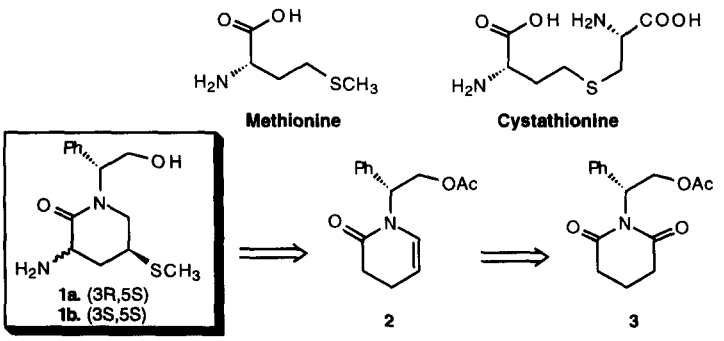
INTRODUCTION

Methionine[1] and cystathionine[2] have shown to inhibit the glutathione (γ-glutamylcysteinylglycine, GSH) efflux of isolated hepatocytes. Hepatic GSH is exclusively synthesized in the cytosol and needs specific carriers for its transport into bile and blood circulation, and thus reach distal extrahepatic organs.[3] It has also been reported that cystathionine is a more powerful GSH transport inhibitor than methionine.[1,2]

In the context of our studies on the synthesis of conformationally restricted pseudopeptides presenting a 3-amino-2-piperidone backbone,[4] we have envisaged the synthesis of 3-amino-5-methylthio-2-piperidones **1** as conformationally restricted analogues of methionine, to be tested as a potential inhibitor of the hepatic transport of glutathione (GSH).[5,6]

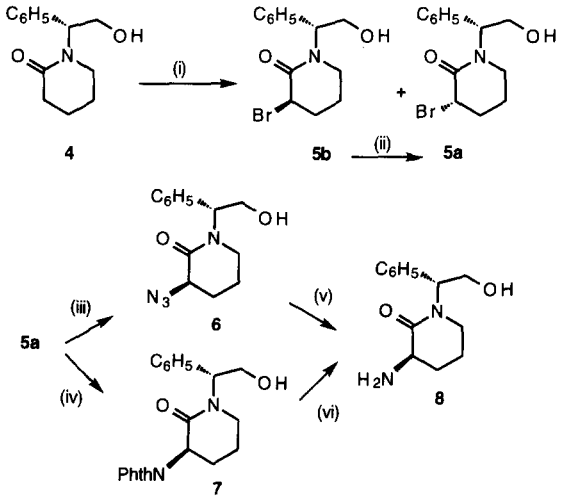
The synthesis of the methionine-phenylglycinol derivatives **1** was planned by subsequent functionalization of positions 5 and 3 of enamide **2**.



Scheme 1

RESULTS AND DISCUSSION

We first studied the introduction of the amino group on 3-position using 2-piperidone **4**[7-9] as a model structure. Treatment of compound **4** with *sec*-BuLi (2.5 equivalents) and Br_2 led to the expected C-3 epimeric mixture of 3-bromolactams **5** (**a**:**b** = 1.3:1). However, the minor isomer **5b** epimerizes to give **5a** on SiO_2 flash column chromatography, and also on standing.[9,10] Subsequent substitution of the bromine atom through treatment of **5a**[11] with NaN_3 or potassium phthalimide led to the corresponding 3-azido- and 3-phthalimido derivatives **6** and **7** as single diastereomers. The reduction of azide **6** was performed by reaction with PPh_3-H_2O at room temperature[12] to give 3-amino-2-piperidone **8** in 16% yield. Amine **8** was also obtained from compound **7** by hydrazinolysis in 65% yield (Scheme 2). The analytical data of bromolactams **5** and aminolactam *(αR,3R)*-**8** were identical to the ones found by Prof. Husson's group.[10]



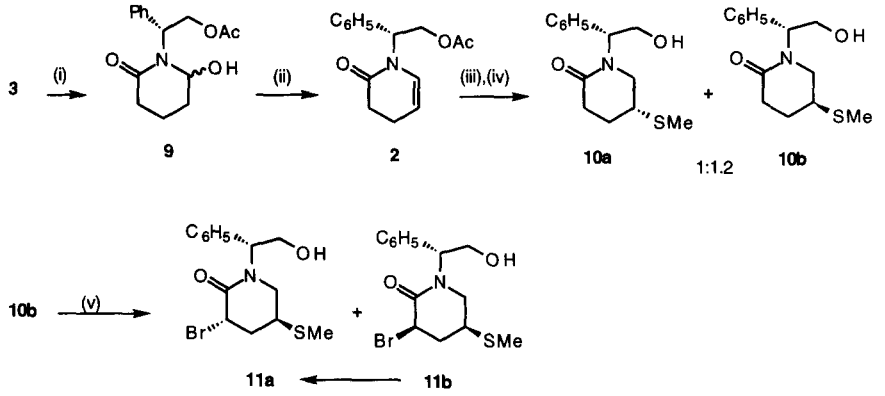
Reagents and conditions: i) 1. *sec*-BuLi (2.5 equivalents), THF, -78°C, 20 min. 2. Br_2 (1.1 equivalent),1 h 45 min (55%); ii) SiO_2 or spontaneously; iii) NaN_3 (2 equivalents), H_2O-DMF/AcOH, room temperature, 7 h, (78%); iv) potassium phthalimide (2 equivalents), DMF, room temperature, 18 h (56%); v) 1. PPh_3 (1.1 equivalents), THF, room temperature, 6 h. 2. H_2O (1.5 equivalents), 15 h (16%); vi) $NH_2NH_2 \cdot H_2O$ (10 equivalents) MeOH, reflux, 1h (70%).

Scheme 2

Enamide **2** was prepared in two steps and 69% yield from imide **3** (Scheme 3).[7] Thus, Super-Hydride® reduction[13] of **3** gave the epimeric mixture of 6-hydroxylactams **9**, which yielded enamide **2** on TFA treatment. Enamide **2** was easily identified by the presence of the olefin signals in its ^1H and ^{13}C NMR spectra (see experimental).

Since enamide **2** can be regarded as a deactivated enamine,[14] its double bond was expected to react as an alkene rather than as an enamine. Indeed, when enamide **2** was treated with electrophiles such as Me_2S_2 or methyl methanethiolsulfonate no reaction was observed, but the AIBN activated free-radical addition of MeSH[15] followed by acid hydrolysis of the acetate group gave the expected anti-Markovnikov diastereomeric 5-methylthiolactams **10a,b** in a ratio of 1:1.2. The most characteristic ^1H NMR data of mercaptane **10a** were a singlet at δ 1.96 (SMe), a double doublet at δ 3.20 (6-H_e), and a double doublet at δ 3.11 (6-H_a) whose

coupling constants (J = 11 and 7 Hz) indicated that the C-5 SMe group adopted an axial disposition. The ^{1}H NMR signals for isomer **10b** were a singlet at δ 1.90 (SMe), a double doublet at δ 3.47 (6-H_e) and a double doublet at δ 2.88 (6-H_a, J = 12 and 7 Hz), which indicated that the C-5 SMe group was also axially disposed.



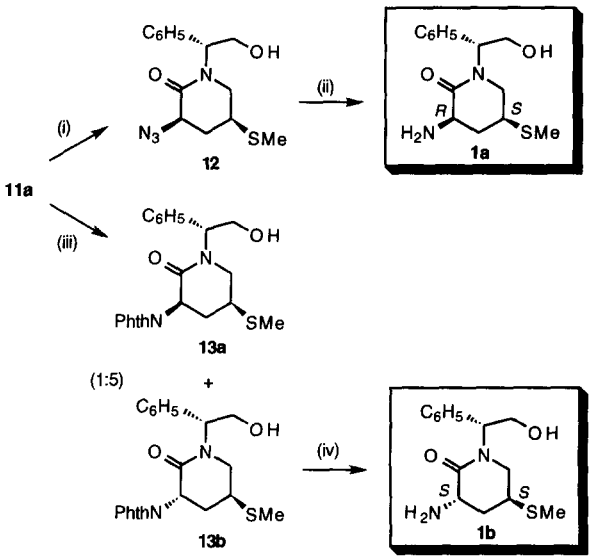
Reagents and conditions: i) $LiBHEt_3$ (1.5 equivalents), THF, -78°C, 2 h; ii) TFA, CH_2Cl_2, room temperature, 30 min (69% two steps); iii) MeSH (10 equivalents), AIBN (catalytic), THF, -78°C, 15 h (62%); iv) 5% aqueous KOH, THF, reflux, 3 h (98%); v) *sec*-BuLi (2.5 equivalents), THF, -78°C, 20 min. 2. Br_2 (1.1 equivalents),1 min 45 sec (45%).

Scheme 3

The introduction of the amino group on 3-position of compound **10b** was then carried out following the procedure shown in Scheme 2. Thus, the bromination of compound **10b** yielded a 3:1 diastereomeric mixture of bromides **11a,b** (Scheme 3). The major isomer, **11a**, was assigned as 3,5-*trans* isomer on the basis of its spectral data. Thus, the axial proton on C-6 appeared at δ 2.89 as a double doublet of J = 12 and 10 Hz, showing that the C-5 SMe group was equatorial. The signal corresponding to 3-H was a narrow triplet (J = 5 Hz) at δ 4.64, indicating that the bromine atom is axially disposed. In addition, no 2D nOe correlation was observed between 3-H and 5-H. Since the bromination gave mainly the *3S* configuration, we deduced that compound **11a** was *(3S,5S)*. By comparison, the minor isomer **11b** was assigned as the 3,5-*cis* isomer, i.e. *(3R,5S)*. Subsequent substitution of the bromine atom through treatment of **11a** with NaN_3 led to the corresponding 3-azido derivative **12** as a single diastereomer in 70% yield. The ^{1}H NMR data of compound **12** showed that the substituents on C-3 and C-5 were *cis*, and therefore *(3R,5S)*, as expected. The diagnostic signals in this case were the triple doublet corresponding to the axial proton on C-4 (δ 1.65, J = 12 and 11 Hz) and the double doublet corresponding to the equatorial C-6 proton (δ 3.42, J = 12 and 5 Hz), respectively. The Ph_3P-H_2O reduction of compound **12** yielded the target aminolactam **1a**. The structural assignment of compound **1a** was again inferred from the ^{1}H NMR data to be the *(3R,5S)*-3-amino-5-methylthio derivative, with both substituents equatorially disposed.

Surprisingly, when bromide **11a** was treated with potassium phthalimide we obtained a 5:1 diastereomeric mixture of phthalimidolactams **13**, from which the major isomer **13b** was isolated pure. According to its ^{1}H NMR spectrum, compound **13b** showed a 3,5-*trans* relationship. Thus, the axial proton on C-6 appeared as a broad doublet (J = 13 Hz), which implied that the SMe group was in an axial disposition,

and 3-H proton was a double doublet at δ 5.17 (J = 11 and 8 Hz), indicating that the phthalimido group was equatorial. This result can only be explained if the SMe substituent prefers an axial disposition, as it does in compounds **10**, which would oblige an epimerization of C-3 to give an equatorial disposition to the bulkiest phthalimido substituent, and therefore, a *(3S,5S)* stereochemistry. Hydrazinolysis of compound **13b** yielded compound **1b**, which was assigned on the basis of its spectral data



Reagents and conditions: i) NaN_3 (2 equivalents), H_2O-DMF/AcOH, room temperature, 7 h, (70%); ii) 1. PPh_3 (1.1 equivalents), THF, room temperature, 12 h. 2. H_2O (1.5 equivalents), 6 h (30%); iii) potassium phthalimide (1.5 equivalents), DMF, room temperature, 24 h, (64%); iv) $NH_2NH_2.H_2O$ (10 equivalents), MeOH, reflux, 3.5 h (73%).

Scheme 4

CONCLUSION

The application of compounds **1a** and **1b** as inhibitors of the hepatic transport of GSH in relation with other known thioether aminoacids is currently under way, both on isolated rat hepatocytes and on oocytes from *Xenopus Laevis* expressing the sinusoidal transport system of GSH.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, SDS). TLC was performed on SiO_2 (silica gel 60 F_{254}, Macherey-Nagel) and developed with the solvent

described in each case for flash chromatography. The spots were located by UV light and Dragendorff or hexachloroplatinate reagent. Optical rotations have been measured with a Perkin-Elmer 241 polarimeter. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

***(αR,3RS)*-3-Bromo-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-ones (5a,b).** To a solution of piperidone **4**[7] (500 mg, 2.28 mmol) in dry THF (25 ml), cooled at -78°C, *sec*-Buli (5.3 ml, 6.84 mmol) was added. After 20 min, cold Br_2 (25 ml, 0.45 mmol) was added dropwise. The resulting mixture was stirred for 2 min 15 sec at -78°C and the reaction was quenched with aqueous NH_4Cl. The solvent was evaporated and the residue, dissolved in CH_2Cl_2, was washed with brine. The organic extracts were dried and evaporated to yield a mixture of *(αR, 3S)*-**5a** and *(αR, 3R)*-**5b**, which were isolated pure by flash chromatography (SiO_2, AcOEt-hexane, 1:2). **Bromolactam *(αR,3S)*-5a** (300 mg, 44%): $[\alpha]_D$ = -112 (c = 0.8, MeOH); IR (NaCl) 3400 (OH), 1650 (CO) cm^{-1}; ^1H NMR (500 MHz) 1.75 (dm, *J* = 14 Hz, 1H, 5-H_e), 2.10 (m, 1H, 5-H_a), 2.23 (dm, *J* = 14 Hz, 1H, 4-H_e), 2.31 (tt, *J* = 14 and 4 Hz, 1H, 4-H_a), 3.08 (dt, *J* = 12 and 4 Hz, 1H, 6-H_e), 3.29 (td, *J* = 12 and 4 Hz, 1H, 6-H_a), 4.06 (dd, *J* = 11.5 and 10 Hz, 1H, β-H_A), 4.19 (dd, *J* = 11.5 and 5 Hz, 1H, β-H_B), 4.66 (t, *J* = 4 Hz, 1H, 3-H_e), 5.83 (dd, *J* = 10 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 18.7 (C-5), 30.9 (C-4), 42.3 (C-6), 45.9 (C-3), 57.5 (C-α), 60.3 (C-β), 127.3 (Ph-*o*), 127.7 (Ph-*p*), 128.5 (Ph-*m*), 136.5 (C-*ipso*), 168.0 (C-2); EIMS *m/z* (%) 299 (M^++1, 1), 297 (M^+-1, 1), 268 (99), 266 (100), 188 (54), 186 (60), 91 (60). Anal. Calcd for $C_{13}H_{16}BrNO_2$: C, 52.52; H, 5.43; N, 4.71; Br, 26.57. Found: C, 52.36; H, 5.37; N, 4.69; Br, 26.82.

Bromolactam *(αR, 3R)*-5b (106 mg, 15%): ^1H NMR 1.65 (m, 1H, 5-H_e), 2.15 (m, 3H, 4-H and 5-H_a), 2.95 (m, 1H, 6-H_e), 3.30 (m, 1H, 6-H_a), 3.60 (br s, 1H, OH), 4.05 (m, 2H, β-H), 4.60 (m, 1H, 3-H), 5.60 (dd, *J* = 11 and 9 Hz, 1H, α-H), 7.15-7.35 (m, 5H, Ph-H); ^{13}C NMR 19.3 (C-5), 30.8 (C-4), 43.9 (C-6), 45.7 (C-3), 59.9 (C-α), 61.3 (C-β), 127.8 (Ph-*o*), 127.9 (Ph-*p*), 128.7 (Ph-*m*), 136.0 (Ph-*ipso*), 167.9 (C-2); EIMS *m/z* (%) 299 (M^++2, 21), 298 (M^+, 21), 268 (100), 266 (99), 200 (87), 186 (64), 159 (38), 91 (67), 77 (39).

Pure isomers **5a** and **5b** epimerize in solution to give a 2:1 mixture of **5a:5b**. Epimerization of **5b** is particularly quick.

***(αR,3R)*-3-Azido-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one (6).** To a solution of pure bromide **5a** (1.05 g, 3.53 mmol) in DMF (40 ml) containing AcOH (1.8 ml), cooled at 0°C, a solution of NaN_3 (459 mg, 7.1 mmol) in H_2O (1.8 ml) was added. The resulting mixture was stirred for 7 h at room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried and evaporated to yield azidopiperidone **6** (715 mg, 78%), which were isolated by flash chromatography (SiO_2, AcOEt-hexane, 1:2): $[\alpha]_D$ = +33.5 (c = 1, $CHCl_3$); IR (NaCl) 3500 (OH), 2103 (N_3), 1639 (CO) cm^{-1}; ^1H NMR 1.65 (m, 1H, 5-H), 1.75 (m, 1H, 5-H), 1.90 (m, 1H, 4-H), 2.05 (m, 1H, 4-H), 2.98 (dt, *J* = 12 and 5 Hz, 1H, 6-H_e), 3.14 (br s, 1H, OH), 3.26 (ddd, *J* = 12, 8 and 4 Hz, 1H, 6-H_a), 4.15 (m, 3H, β-H and 3-H), 5.80 (dd, *J* = 11 and 7 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 20.2 (C-5), 27.3 (C-4), 43.3 (C-6), 59.1 (C-3), 59.7 (C-α), 61.3 (C-β), 127.7 (Ph-*o*), 128.0 (Ph-*p*), 128.8 (Ph-*m*), 136.3 (C-*ipso*), 169.2 (C-2); EIMS *m/z* (%) 260 (M^+, 1), 229 (99), 200 (71), 173 (24), 146 (21), 103 (88), 91 (100). Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.97; H, 6.20; N, 21.53. Found: C, 59.67; H, 6.34; N, 21.48.

***(αR,3R)*-*N*-(2-Hydroxy-1-phenylethyl)-3-phthalimidopiperidin-2-one (7).** To a solution of bromide **5a** (100 mg, 0.33 mmol) in DMF (2 ml), a solution of potassium phthalimide (124 mg, 0.67 mmol) in DMF (1.5 ml) was added. After stirring for 18 h at room temperature, the mixture was washed with brine. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts, dried and evaporated, were flash chromatographed (AcOEt-hexane, 2:1) to yield phthalimidopiperidone **7** (67 mg, 56%): $[\alpha]_D$ = -49.5 (c = 1, $CHCl_3$); IR (NaCl) 3453 (OH), 1716 (CO), 1648 (CO) cm^{-1}; ^1H NMR 1.70 (m, 1H, 5-H_a), 1.90 (dm, *J* = 14 Hz, 1H, 5-H_e), 2.65 (m, 1H, 4-H_e), 2.21 (qd, *J* = 12 and 3 Hz, 1H, 4-H_a), 2.93 (br s, 1H, OH), 3.00 (br d, *J* = 12 Hz, 1H, 6-H_e), 3.36 (td, *J* = 12 and 4 Hz, 1H, 6-H_a), 4.10 (m, 2H, β-H), 4.80 (dd, *J* = 11 and 7 Hz, 1H, 3-H_a), 5.80 (dd, *J* = 8 and 6 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H), 7.70-7.90 (m, 4H, Ar-H); ^{13}C NMR 21.8 (C-5), 26.7 (C-4), 43.1 (C-6), 49.9 (C-3), 58.9 (C-α), 61.1 (C-β), 123.4 (Phth-α), 127.6 (Ph-*o*), 127.8 (Ph-*p*), 128.6 (Ph-*m*), 131.9 (Phth-quaternary), 134.0 (Phth-β), 136.5 (C-*ipso*), 167.4 (CO), 167.8 (CO); EIMS *m/z* (%) 365 (M^++1, 1), 333 (96), 305 (75), 200 (87), 182 (41), 159 (100). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.23; H, 5.49; N, 7.69. Found: C, 69.21; H, 5.51; N, 7.61.

***(αR,3R)*-3-Amino-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one (8).** **Procedure A:** To a solution of azide **6** (100 mg, 0.38 mmol) in THF (5 ml), PPh_3 (121 mg, 0.46 mmol) was added. The resulting mixture was stirred for 6 h at room temperature, H_2O (1.5 equivalents) was added, and the solution was stirred at room temperature overnight. The solvent was evaporated and the residue, dissolved in CH_2Cl_2, was washed with ice-cold 2N HCl. The acid aqueous solution was washed with CH_2Cl_2, basified with $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts, dried and evaporated, yielded pure 3-aminopiperidone **8** (15 mg, 16%): $[\alpha]_D$ = -72.1 (c = 1, $CHCl_3$); IR (NaCl) 3350 (OH), 3349 and 3302 (NH_2), 1635 (CO) cm^{-1}; ^1H NMR 1.60 (m, 2H, 5-H), 1.86 (m, 1H, 4-H), 2.14 (m, 1H, 4-H), 2.30 (br s, 3H, NH_2 and OH), 2.93 (dt, *J* = 12 and 3.5 Hz, 1H, 6-H_e), 3.19 (ddd, *J* = 12, 7 and 2 Hz, 1H, 6-H_a), 3.40 (br dd, *J* = 12 and 6 Hz, 1H, 3-H_a), 4.04 (dd, *J* = 12 and 9 Hz, 1H, β-H_A), 4.10 (dd, *J* = 12 and 5 Hz, 1H, β-H_B), 5.73 (dd, *J* = 9 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 21.2 (C-5), 29.4 (C-4), 42.9 (C-6), 52.2 (C-3), 58.0 (C-α), 60.8 (C-β), 127.5 (Ph-*o*), 127.7 (Ph-*p*), 128.6 (Ph-*m*), 137.0 (C-*ipso*), 174.1 (CO); EIMS *m/z* (%) 235 (M^++1, 3), 203 (42), 175 (48), 106 (32), 77 (21), 70 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.66; H, 7.69; N, 11.96. Found: C, 66.54; H, 7.65; N, 11.91.

Procedure B: To a solution of phthalimide **7** (121 mg, 0.35 mmol) in MeOH (6 ml), $NH_2NH_2 \cdot H_2O$ (0.22 ml, 3.54 mmol) was added. The resulting mixture was refluxed for 1 h. The solvent was evaporated and the residue, dissolved in CH_2Cl_2, was washed with 2.6N KOH. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried and evaporated to yield pure amine **8** (55 mg, 70%).

***(αR)*-*N*-(2-Acetoxy-1-phenylethyl)-Δ^5-piperidin-2-one (2).** To a solution of imide **3**[9] (1 g, 3.64 mmol) in dry THF (50 ml) cooled at -78°C, $LiBHEt_3$ (5.5 ml, 5.46 mmol) was added. After stirring for 2.5 h, the reaction was quenched with aqueous $NaHCO_3$. The solvent was evaporated and the residue, dissolved in dry CH_2Cl_2, was treated with TFA (3 ml) for 1.5 h at room temperature and the reaction was quenched with aqueous $NaHCO_3$. The resulting mixture was diluted with CH_2Cl_2 and washed with brine. The organic extracts were dried and evaporated to give an oil, which after flash chromatography (AcOEt:hexane, 1:1)

yielded *N*-(2-acetoxy-1-phenylethyl)-6-hydroxypiperidin-2-ones[9] **9** (150 mg, 15%) and enamide **2** (650 mg, 69%): $[\alpha]_D$ = -91.8 (c = 1, $CHCl_3$); IR (NaCl) 1745 (CO), 1675 (CO), 1600 (C=C) cm^{-1}; ^1H NMR 2.05 (s, 3H, CH_3), 2.30 (m, 2H, 4-H), 2.58 (dd, *J* = 8 and 1.5 Hz, 1H, 3-H), 2.61 (dd, *J* = 8 and 2.5 Hz, 1H, 3-H), 4.51 (dd, *J* = 12 and 8 Hz, 1H, β-H_A), 4.65 (dd, *J* = 12 and 5 Hz, 1H, β-H_B), 5.15 (dt, *J* = 8 and 4 Hz, 1H, 5-H), 5.95 (d, *J* = 8 Hz, 1H, 6-H), 6.12 (dd, *J* = 8 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 19.7 (C-4), 20.7 (*C*H_3CO), 31.5 (C-3), 52.7 (C-α), 62.6 (C-β), 106.8 (C-5), 125.7 (C-6), 127.3 (Ph-*o*), 127.8 (Ph-*p*), 128.6 (Ph-*m*), 136.2 (C-*ipso*), 169.5 (CON), 170.5 (COO); EIMS *m/z* (%) 259 (M^+, 10), 215 (49), 199 (67), 186 (84), 159 (89), 91 (100). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.56; N, 5.40. Found: C, 69.40; H, 6.55; N, 5.51.

***(αR,5RS)*-*N*-(2-Hydroxy-1-phenylethyl)-5-methylthiopiperidin-2-ones (10a,b).** To a solution of enamide **2** (1.7 g, 6.57 mmol) in dry THF (20 ml) cooled at -78°C, CH_3SH (4.3 ml, 73.4 mmol) and catalytic AIBN were added. The solution was stirred for 30 min at -78°C and at room temperature overnight. The solvent was evaporated and the residue was filtered through SiO_2 to yield the epimeric mixture of the acetates of **10** (1.26 g). To a solution of the epimeric mixture in dry THF (45 ml) 5% aqueous KOH (10 ml) was added, and the mixture was refluxed for 1.5 h and neutralized with 3N HCl. The solvent was evaporated and the residue, dissolved in CH_2Cl_2, was washed with aqueous $NaHCO_3$ and with brine. The organic extracts were dried and evaporated to yield, after flash chromatography (AcOEt; AcOEt:MeOH 1:1), a 1:1.2 mixture of mercaptanes **10a** and **10b**. ***(αR,5R)*-10a** (477 mg, 27%): m.p. 54.1-54.3°C (^{i}PrOH), $[\alpha]_D$ = -25.3 (c = 1, $CHCl_3$); IR (NaCl) 3375 (OH), 1623 (CO), 1440 (CS) cm^{-1}; ^1H NMR 1.70 (m, 1H, 4-H_a), 1.96 (s, 3H, SMe), 2.11 (m, 1H, 4-H_e), 2.51 (ddd, *J* = 17, 9 and 7 Hz, 1H, 3-H_a), 2.68 (ddd, *J* = 17, 7 and 5.5 Hz, 1H, 3-H_e), 2.84 (m, 1H, 5-H), 3.11 (dd, *J* = 11 and 7 Hz, 1H, 6-H_a), 3.20 (dd, *J* = 11 and 4 Hz, 1H, 6-H_e), 4.08 (dd, *J* = 10 and 9 Hz, 1H, β-H_A), 4.15 (dd, *J* = 10 and 5 Hz, 1H, β-H_B), 5.87 (dd, *J* = 9 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 13.8 (SMe), 20.8 (C-4), 30.9 (C-3), 40.5 (C-5), 47.3 (C-6), 57.8 (C-α), 61.1 (C-β), 127.6 (Ph-*o*), 127.8 (Ph-*p*), 128.6 (Ph-*m*), 136.6 (C-*ipso*), 170.7 (CO); EIMS *m/z* (%) 265 (M^+, 1), 247 (20), 234 (100), 201 (15), 186 (18). Anal. Calcd for $C_{14}H_{19}NSO_2$: C, 63.37; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.40; H, 7.24; N, 5.21; S, 11.90.

***(αR,5S)*-10b** (583 mg, 33.%): m.p. 95.2-95.4°C (^{i}PrOH:pentane, 9:1), $[\alpha]_D$ = -43.8 (c = 1, $CHCl_3$); IR (NaCl) 3420 (OH), 1614 (CO), 1435 (CS) cm^{-1}; ^1H NMR 1.80 (m, 1H, 4-H_a), 1.90 (s, 3H, SMe), 2.23 (m, 1H, 4-H_e), 2.50 (dt, *J* = 17 and 7 Hz, 1H, 3-H_a), 2.66 (dt, *J* = 17 and 7 Hz, 1H, 3-H_e), 2.88 (dd, *J* = 12 and 7 Hz, 1H, 6-H_a), 3.01 (m, 1H, 5-H), 3.47 (dd, *J* = 12 and 4 Hz, 1H, 6-H_e), 4.06 (dd, *J* = 12 and 9 Hz, 1H, β-H_A), 4.13 (dd, *J* = 12 and 5 Hz, 1H, β-H_B), 5.90 (dd, *J* = 9 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 13.6 (SMe), 26.5 (C-4), 30.5 (C-3), 40.1 (C-5), 46.8 (C-6), 57.5 (C-α), 60.8 (C-β), 127.7 (Ph-*o*), 128.5 (Ph-*p*), 128.9 (Ph-*m*), 136.4 (C-*ipso*), 170.7 (CO); EIMS *m/z* (%) 265 (M^+, 1), 247 (25), 234 (100), 201 (20), 186 (15). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22; N, 5.28; S, 12.08 Found: C, 63.40; H, 7.24; N, 5.21; S, 11.90.

***(αR,3RS,5R)*-3-Bromo-*N*-(2-hydroxy-1-phenylethyl)-5-methylthiopiperidin-2-ones (11a,b).** Operating as for the preparation of compounds **5**, from thioether **10b** (550 mg, 2.08 mmol), dry THF (15 ml), *sec*-BuLi (4 ml, 5.19 mmol), and Br_2 (0.13 mL, 2.29 mmol) a mixture of **11a** and **11b** was obtained, which was flash chromatographed (AcOEt-hexane, 2:1). ***(αR,3S,5S)*-11a** (220 mg, 31%): $[\alpha]_D$ = -21.7 (c = 1.25, $CHCl_3$); IR

(NaCl) 3405 (OH), 1648 (CO), 1437 (C-S) cm^{-1}; ^1H NMR (500 MHz) 1.94 (s, 3H, SMe), 2.20 (ddd, J = 14, 10 and 5 Hz, 1H, 4-H_a), 2.45 (dt, J = 14 and 4 Hz, 1H, 4-H_e), 2.89 (dd, J = 12 and 10 Hz, 1H, 6-H_a), 3.32 (m, 1H, 5-H), 3.52 (dd, J = 12 and 5 Hz, 1H, 6-H_e), 4.09 (m, 2H, β-H), 4.64 (t, J = 5 Hz, 1H, 3-H), 5.57 (dd, J = 8 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 12.6 (SMe), 35.8 (C-5), 36.1 (C-4), 43.4 (C-3), 47.1 (C-6), 58.4 (C-α), 60.1 (C-β), 126.9 (Ph-*o*), 127.1 (Ph-*p*), 127.8 (Ph-*m*), 134.8 (C-*ipso*), 166.0 (CO); EIMS *m/z* (%) 345 (M^++1, 1), 343 (M^+-1, 1), 314 and 312 (100), 268 (10), 246 (70), 234 (60), 91 (90). Anal. Calcd for $C_{14}H_{18}NSBrO_2$: C, 48.98; H, 5.29; N, 4.08; Br, 23.01. Found: C, 48.78; H, 5.27; N, 4.12; Br, 22.97.

***(αR,3R,5S)*-11b** (100 mg, 14%): IR (NaCl) 3395 (OH), 1649 (CO), 1450 (C-S) cm^{-1}; ^1H NMR 1.97 (s, 3H, SMe), 2.15 (m, 1H, 4-H), 2.28 (m, 1H, 4-H), 2.95 -3.10 (m, 2H, 6-H_a and 5-H), 3.40 (dd, J = 12 and 4 Hz, 1H, 6-H_e), 4.00-4.20 (m, 2H, β-H), 4.59 (dd, J = 8.5 and 7 Hz, 1H, 3-H), 5.73 (dd, J = 9 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 13.6 (SMe), 38.5 (C-4), 39.1 (C-5), 44.4 (C-3), 47.9 (C-6), 59.3 (C-α), 60.9 (C-β), 126.9 (Ph-*o*), 128.1 (Ph-*p*), 128.7 (Ph-*m*), 135.8 (C-*ipso*), 167.4 (CO); EIMS *m/z* (%) 345 (M^++1, 1), 343 (M^+-1, 1), 314 and 312 (100), 246 (70), 234 (45), 91 (90).

***(αR,3R,5S)*-3-Azido-*N*-(2-hydroxy-1-phenylethyl)-5-methylthiopiperidin-2-one (12).** Operating as for the preparation of compound **6**, from bromide **11a** (70 mg, 0.20 mmol) in DMF-AcOH ((6:4, 2.1 ml), NaN_3 (26 mg, 0.40 mmol), and H_2O (0.2 ml), azidolactam **12** (43 mg, 70%) was obtained, after flash chromatography (SiO_2, AcOEt-hexane, 1:1): $[\alpha]_D$ = -57.4 (c = 1, $CHCl_3$); IR (NaCl) 3395 (OH), 2114 (N_3), 1649 (CO), 1445 (C-S) cm^{-1}; ^1H NMR 1.65 (td, J = 12 and 11 Hz, 1H, 4-H_a), 1.99 (s, 3H, SMe), 2.42 (m, 1H, 4-H_e), 2.83 (dd, J = 12 and 10 Hz, 1H, 6-H_a), 3.00 (ddt, J = 12, 11 and 5 Hz, 1H, 5-H_a), 3.42 (dd, J = 12 and 5 Hz, 1H, 6-H_e), 4.15 (d, J = 7 Hz, 2H, β-H), 4.19 (dd, J = 11 and 7 Hz, 1H, 3-H_a), 5.80 (t, J = 7 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 13.5 (SMe), 33.6 (C-4), 37.6 (C-5), 47.5 (C-6), 58.6 (C-3), 58.8 (C-α), 60.9 (C-β), 127.9 (Ph-*o*), 128.2 (Ph-*p*), 128.8 (Ph-*m*), 135.4 (C-*ipso*), 168.9 (CO); EIMS *m/z* (%) 306 (M^+, 1), 275 (75), 246 (34), 198 (12), 91 (100). Anal. Calcd for $C_{14}H_{18}N_4SO_2$: C, 54.88; H, 5.93; N, 18.30. Found: C, 54.79; H, 5.88; N, 18.29.

***(αR,3S,5S)*-*N*-(2-Hydroxy-1-phenylethyl)-5-methylthio-3-phthalimidopiperidin-2-one (13).** Operating as for the preparation of compound **7**, from bromides **11a** (150 mg, 0.44 mmol) and potassium phthalimide (122 mg, 0.66 mmol) in DMF (3 ml), and after 24 h of reaction, a 1:5 diastereomeric mixture of phthalimidolactams **13a,b** was obtained, from which only isomer **13b** was isolated by flash chromatographed (AcOEt-hexane, 2:1). Compound **13b** (115 mg, 64%) m.p. 199-199.7°C(AcOEt); $[\alpha]_D$ = -11.5 (c = 2, $CHCl_3$); IR (NaCl) 3430 (OH), 1717 (CO), 1660 (CO), 1390 (C-S) cm^{-1}; ^1H NMR 1.84 (s, 3H, SMe), 2.29 (m, 1H, 4-H_e), 2.58 (ddd, J = 13, 10 and 4 Hz, 1H, 4-H_a), 3.12 (br d, J = 13 Hz, 1H, 6-H_a), 3.28 (m, 1H, 5-H_e), 3.75 (dd, J = 13 and 3 Hz, 1H, 6-H_e), 4.23 (m, 2H, β-H), 5.17 (dd, J = 11 and 8 Hz, 1H, 3-H_a), 5.98 (dd, J = 8 and 5 Hz, 1H, α-H), 7.25-7.40 (m, 5H, Ph-H), 7.70-7.75 and 7.85-7.90 (2 m, 2H each, Phth-H); ^{13}C NMR 13.9 (SMe), 31.2 (C-4), 39.3 (C-5), 45.9 (C-6), 47.1 (C-3), 58.1 (C-α), 60.9 (C-β), 123.5 (Phth-α), 127.9 (Ph-*o* and Ph-*p*), 128.6 (Ph-*m*), 131.8 (Phth-quaternary), 134.1 (Phth-β), 136.1 (C-*ipso*), 166.7 (CO), 167.7 (CO); EIMS *m/z* (%) 411 (M^++1, 1), 379 (100), 333 (39), 246 (61), 179 (35), 156 (56). Anal. Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82; S, 7.81. Found: C, 64.25; H, 5.36; N, 6.76; S, 7.64.

***(αR,3R,5S)*-3-Amino-*N*-(2-hydroxy-1-phenylethyl)-5-methylthiopiperidin-2-one (1a).** Operating as for the preparation of compound **8**, from azide **12** (80 mg, 0.26 mmol) and PPh_3 (68 mg, 0.26 mmol) in THF (3 ml), and after a preparative chromatography (SiO_2, CH_2Cl_2, MeOH, 95:5), 3-aminolactam **1** (22 mg, 30%) was obtained: $[\alpha]_D$ = -41.7 (c = 0.5, $CHCl_3$); IR (NaCl) 3356 (OH and NH_2), 1629 (CO), 1463 (C-S) cm^{-1}; ^1H NMR 1.55 (q, *J* = 11 Hz, 1H, 4-H_a), 1.95 (s, 3H, SMe), 2.45 (m, 1H, 4-H_e), 2.75 (br s, 3H, NH_2 and OH), 2.90 (dd, *J* = 12 and 11 Hz, 1H, 6-H_a), 3.03 (m, 1H, 5-H_a), 3.45 (dd, *J* = 12 and 6 Hz, 1H, 6-H_e), 3.50 (dd, *J* = 10 and 7 Hz, 1H, 3-H_a), 4.05 (m, 2H, β-H), 5.70 (dd, *J* = 9 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ar-H); ^{13}C NMR 13.4 (SMe), 35.8 (C-4), 38.2 (C-5), 47.9 (C-6), 51.7 (C-3), 58.9 (C-α), 60.9 (C-β), 127.6 (Ph-*p*), 128.0 (Ph-*o*), 128.7 (Ph-*m*), 136.1 (C-*ipso*), 173.6 (CO); EIMS *m/z* (%) 280 (M^+, 4), 249 (22), 233 (27), 173 (44), 159 (100). Anal. Calcd for $C_{14}H_{20}N_2SO_2$: C, 59.98; H, 7.20; N, 10.00. Found: C, 60.08; H, 7.21; N, 9.85.

***(αR,3S,5S)*-3-Amino-*N*-(2-hydroxy-1-phenylethyl)-5-methylthiopiperidin-2-one (1b).** Operating as for the preparation of compound **8**, from phthalimide **13** (50 mg, 0.12 mmol) and $NH_2NH_2 \cdot H_2O$ (0.1 ml, 1.2 mmol) in MeOH (1 ml), amine **1b** (25 mg, 73%) was obtained: $[\alpha]_D$ = -25.7 (c = 1, $CHCl_3$); ^1H NMR 1.86 (s, 3H, SMe), 2.01 (ddd, *J* = 13, 10 and 4 Hz, 1H, 4-H_a), 2.21 (dt, *J* = 13 and 7 Hz, 1H, 4-H_e), 2.41 (br s, 3H, NH_2 and OH), 2.96 (dd, *J* = 12.5 and 6 Hz, 1H, 6-H_a), 3.13 (m, 1H, 5-H), 3.50 (dd, *J* = 12.5 and 4 Hz, 1H, 6-H_e), 3.69 (dd, *J* = 10 and 7 Hz, 1H, 3-H), 4.05 (dd, *J* = 11 and 9 Hz, 1H, β-H_A), 4.15 (dd, *J* = 11 and 5 Hz, 1H, β-H_B), 5.82 (dd, *J* = 9 and 5 Hz, 1H, α-H), 7.20-7.40 (m, 5H, Ph-H); ^{13}C NMR 13.9 (SMe), 34.8 (C-4), 38.8 (C-5), 46.4 (C-6), 49.5 (C-3), 50.8 (C-α), 61.1 (C-β), 127.7 (Ph-*o*), 127.9 (Ph-*p*), 128.7 (Ph-*m*), 136.5 (C-*ipso*), and 173.8 (CO); EIMS *m/z* (%) 280 (M^+, 1), 249(18), 233 (22), 173 (51), 159 (100). Anal. Calcd for $C_{14}H_{20}N_2SO_2$: C, 59.98; H, 7.20; N, 10.00; S, 22.83. Found: C, 60.08; H, 7.21; N, 9.85; S, 22.98.

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