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Synthesis and Synthetic Applications of 3-Amino-Δ^5-piperidein-2-ones: Synthesis of Methionine-derived Pseudopeptides

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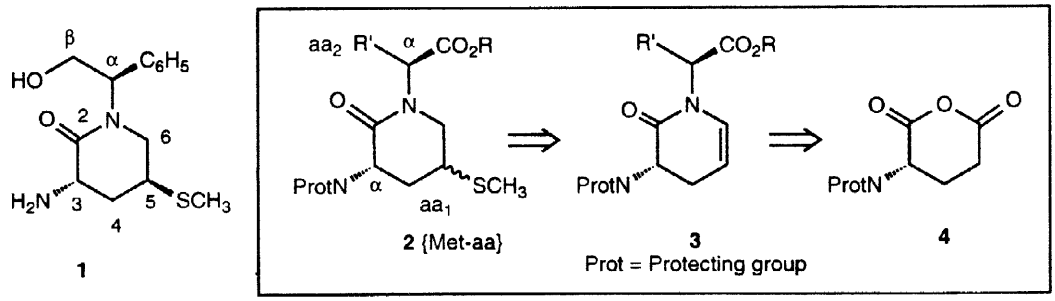
Abstract– A method is described for the efficient preparation of 3-amino-Δ^5-piperidein-2-ones **3**. A synthetic application of enamides **3** has been achieved by methylthiolation on the C5 position to obtain the target methionine-derived pseudopeptides **2**.
Keywords: peptide mimetics, enamides, lactams, piperideinones

Introduction

In the context of our studies on the synthesis of conformationally restricted pseudopeptides[1] presenting a 3-amino-2-piperidone backbone,[2] and more specifically on the preparation of methionine derivatives as potential inhibitors of the hepatic transport of glutathione,[3] we prepared compound **1** (Scheme 1) and its C3 epimer, derived from methionine and (*R*)-phenylglycinol.[4] We now present the synthesis of protected pseudopeptides **2**, with the double purpose of submitting them to pharmacological testing[5] and of studying structure-activity relationships through introduction into longer peptide chains of known activity.[6]



Scheme 1

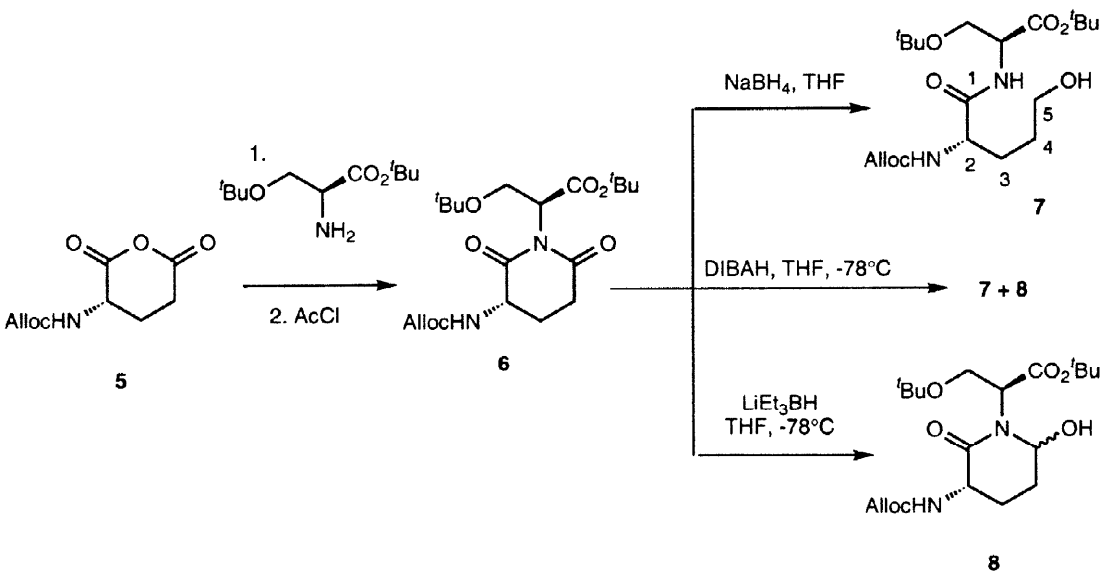
PII: S0040-4020(99)00545-1

For the preparation of **1**, we chose to introduce the SMe group on the C5 of a Δ^5-piperidein-2-one, and to perform the C3 amination in the last steps of the synthesis. However, we could not apply the same strategy to the synthesis of the amino acid derivatives **2** because the C3 amination would be problematic. Thus, the use of a strong base such as *sec*-BuLi would racemize the amino acid labelled aa_2 in scheme 1, and the need for a free hydroxyl group on the side chain of the lactam nitrogen atom to obtain the C3 enolate conveniently,[7] would limit the range of amino acids aa_2.

We therefore envisaged the use of a 3-amino-Δ^5-piperidein-2-one type **3** as our new building block. In principle, compounds **3** could be easily prepared from commercially available glutamic acid, with the advantage of presenting the amino group in a prefixed configuration, and with the possibility of functionalising not only the C5 but also the C4 and C6 positions.

Results and Discussion

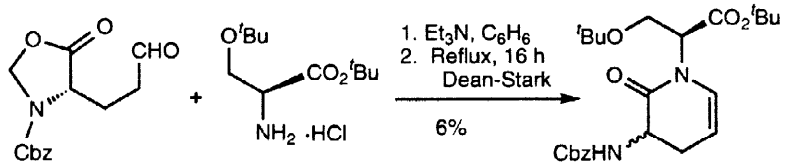
We chose to use di-*tert*-butylserine as the aa_2 because of its side chain functionality, and, in light of our previous work,[2c,4] we first planned to prepare the corresponding enamide **3** (Prot = Alloc; R = ^{t}Bu; R' = CH_2O^tBu) by reduction of imide **6**. Imide **6** was prepared by reaction of anhydride **5**[8] with di-*tert*-butylserine with final addition of AcCl (Scheme 2). The subsequent reduction of imide **6** with $NaBH_4$ in THF yielded alcohol **7** as the only product, derived from the reduction of the intermediate open-chain aldehyde.[9] Alcohol **7** was identified by the presence of two broad doublets at δ 5.80 and 6.98 in its ^{1}H NMR spectrum, corresponding to the amide and carbamate NH protons respectively, and by the multiplet centered at δ 3.70 due to the methylene group bearing the alcohol. The ^{13}C NMR spectrum also showed the presence of the C5 methylene group (δ 62.1), and the structure was confirmed by mass spectrometry.



Scheme 2

Treatment of **6** with DIBAH gave an equimolar mixture of alcohol **7** and 6-hydroxylactams **8**, which were separated by column chromatography. Hydroxylactams **8** were obtained as a mixture of the C6 epimers, as shown by the presence of split signals in the ^{13}C NMR spectrum. The most relevant signals for assigning the structure were: i) the methine carbon at δ 83.2, which corresponded to C6 and indicated that the reduction had occurred; ii) the quaternary carbon of the *tert*-butoxycarbonyl at δ 81.6 and 82.4; and iii) the quaternary carbon of the *tert*-butoxy group at δ 72.9. When $LiEt_3BH$ was used as the reducing agent we obtained the epimeric mixture of hydroxylactams **8** as the only isolable products. Unfortunately, all attempts to eliminate the C6 hydroxyl group of compound **8** to obtain the desired enamide type **3** were unsuccessful, and we recovered only the starting material or decomposition products when the reaction conditions were forced.[10]

In view of these results we decided to use aldehyde **9**[11] as the Δ^5-piperidein-2-one precursor, by condensing it directly with di-*tert*-butylserine (Scheme 3). The reaction in refluxing C_6H_6 in a Dean-Stark trap in the presence of Et_3N (1 equivalent) gave the expected enamide, **11**, but in very low yield (6%), and as a 4:1 mixture of epimers on C3. The most characteristic spectral data of compounds **11** were the signals at δ 5.21 and 6.50 in the ^1H NMR spectrum, corresponding to the double bond protons, and the olefinic methine carbons at δ 104.2 (C5) and 129.1 (C6) in the ^{13}C NMR.



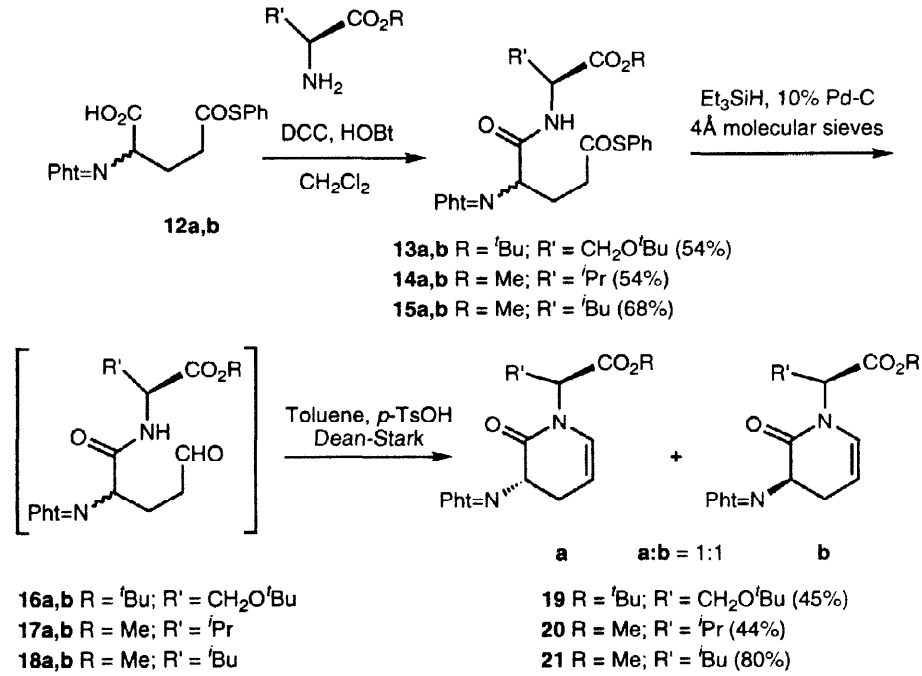
9 **10** **11a,b**

Cbz = benzyloxycarbonyl **a:b** = 4:1

Scheme 3

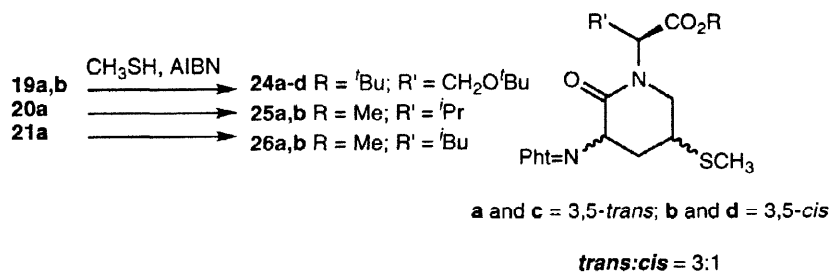
As an alternative, we coupled the racemic phthaloylthioester **12**[12] with di-*tert*-butylserine using the standard DCC-HOBt conditions, to obtain amides **13a,b** in 54% yield (Scheme 4). The subsequent reduction of the thioester with Et_3SiH and 10% Pd-C[13] yielded the corresponding aldehyde that was directly cyclized using *p*-TsOH to obtain enamides **19a,b** in 45% yield.[14,15] The most relevant data for the structural assignment of the enamides were the double bond NMR signals (see Experimental) and the absence of the thioester phenyl ring.

In order to establish the validity of the method, we applied the three-step sequence to prepare the {Met-Val} and {Met-Leu} pseudopeptides. The best results were obtained using a mixture of DMF and CH_2Cl_2 as the solvent for the coupling reaction to obtain amides **14** and **15**. The following reduction and cyclisation gave the corresponding enamides **20** and **21** as equimolar mixtures of the C3 epimers. The two diastereomers of both **20** and **21** were separated by column chromatography, and all enamides showed the characteristic double bond signals in the NMR spectra (δ_H ~ 5.3 and 6.2; δ_C ~ 105 and 126).[15]



Scheme 4

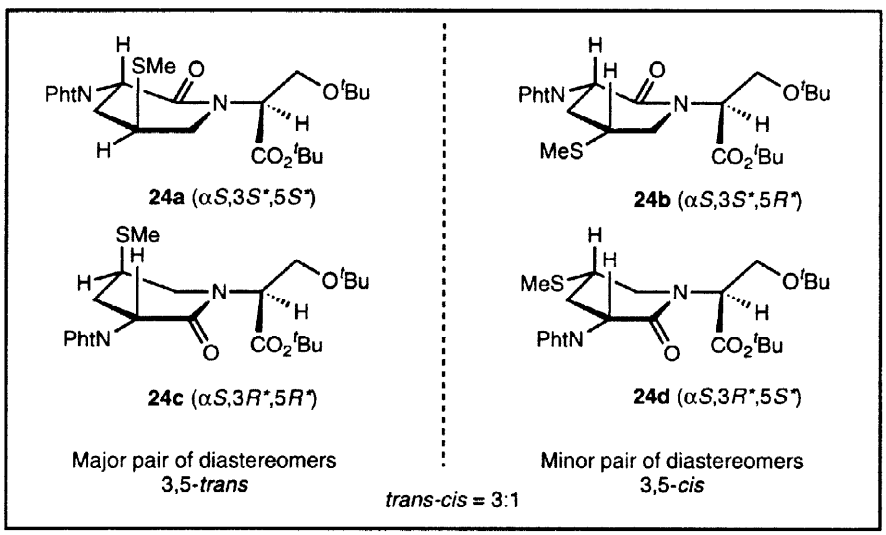
Once the synthesis of enamides of type **3** had been established, we proceeded to the preparation of the {Met-aa} derivatives **24-26** (Scheme 5). The methylthio group was introduced by treatment of enamides **19a,b**, **20a**, and **21a** with MeSH in the presence of AIBN.[4] The resulting type **2** piperidones, **24-26**, showed the characteristic methyl group (δ_H ~2.2; δ_C ~ 14), and the loss of the double bond. From the four possible diastereomers of {Met-Ser} lactams **24**[15] (Scheme 6), only two were observed in the NMR spectra, in the proportion 3:1. This indicated that each pair, the 3,5-*trans*- (**a** and **c**) and the 3,5-*cis*-substituted (**b** and **d**), adopts the same ring conformation.



Scheme 5

In the ^{1}H NMR spectrum of compounds **24** (*trans*:*cis* = 3:1), the 3-H proton appeared as a double doublet (J = 10 and 8 Hz), indicating that it is pseudoaxially disposed in both *cis* and *trans* diastereomers. A sample of only the major *trans* pair of diastereomers, **a** and **c**, was obtained by column chromatography. The signal corresponding to the pseudoaxial 4-H proton of these isomers was a double doublet of doublets (J =

13, 10, and 6 Hz), which, together with the multiplicity observed for the corresponding 5-H proton (a double triplet of J = 7 and 6 Hz) indicated that the SMe group is pseudoaxial. Hence, we identified the major pair of piperidones **24a** and **24c** as the 3,5-*trans* diastereomers, and the minor pair as the 3,5-*cis*.[16]



Scheme 6

The methylthiolation of pure **20a** in a sealed tube yielded a 3:1 mixture of piperidones *trans*-**25a** and *cis*-**25b** in 80% yield,[15] from which the major isomer was obtained pure by column chromatography. As in the case of compound **20a**, the relative disposition of the substituents was inferred from the signal multiplicity of the 3-H, the axial 4-H, and 5-H protons in the ^{1}H NMR spectrum, which clearly indicated that the phthalimido group was equatorial and that the methylthio substituent was axial in the major *trans* isomer. Similarly, the methylthiolation of pure **21a**[15] gave a 3:1 proportion of *trans*-**26a** and *cis*-**26b**. Since the 3:1 proportion is maintained regardless of the aa_2, we think that the steric hindrance that the C3 phthalimido group exerts on one side of the piperideinone ring is responsible for the stereoselection observed.

Compounds **24-26** are currently being tested as potential inhibitors of the hepatic transport of glutathione. Enamides of type **3** should allow us to functionalise the lactam ring on positions C4, C5, and C6 in the near future, and therefore provide access to a wide range of 3-aminopiperidin-2-one pseudodipeptides.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus. Optical rotations were measured with a Perkin-Elmer 241 polarimeter, at 23°C. ^{1}H 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, either by chemical ionization (CIMS) or electronic impact

(EIMS). Flash column chromatography was carried out on SiO_2 (silica gel 60, 35-70 μm, SDS). TLC was performed on SiO_2 (silica gel 60 F254, Macherey-Nagel) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and $KMnO_4$. 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 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica CID, Barcelona.

(α*S*,3*S*)-3-Allyloxycarbonylamino-*N*-[2-*tert*-butoxy-1-(*tert*-butoxycarbonyl)ethyl]piperidin-2,6-dione (6). To a solution of commercial L-glutamic acid (6 g, 40.3 mmol) in dioxane-H_2O (2:1, 120 ml) at 0°C, 2N NaOH (40 ml) was added (pH = 10). A solution of allyl chloroformate (5.2 ml, 48.9 mmol) in dioxane (20 ml) was slowly added, and the pH was readjusted with 2N NaOH. The reaction was stirred at 0°C for 1 h and at room temperature for 4 days. The reaction mixture was cooled to 0°C, acidified by addition of 1N aqueous $NaHSO_4$, and extracted with AcOEt. The organic extracts, dried and evaporated, yielded ***(S)-N*-allyloxycarbonylglutamic acid** as a yellow oil (7.82 g, 84%), which was used without further purification. IR ($CHCl_3$) 3400-2400 (CO_2H), 1730 (br s, CO), 1540 (C=C) cm^{-1}; ^1H NMR 2.20-2.30 (m, 2H, β-H), 2.50-2.60 (m, 2H, γ-H), 4.47 (q, J = 6 Hz, 1H, α-H), 4.58 (d, J = 5 Hz, 2H, OCH_2), 5.23 (dd, J = 10 and 1 Hz, 1H, CH=CH_A), 5.32 (br d, J = 17 Hz, 1H, CH=CH_B), 5.49 (br d, J = 6 Hz, 1H, NH), 5.85-5.98 (m, 1H, CH=CH_2); ^{13}C NMR 26.9 (C-β), 29.6 (C-γ), 52.8 (C-α), 66.1 (OCH_2), 118.1 (CH=CH_2), 132.3 (CH=CH_2), 155.4 (NHCOAlloc), 176.0 and 177.9 (CO acids). CIMS *m/z* 232 (M^++1), 260 (M^++29).

To a solution of the allyloxycarbonylglutamic acid (10 g, 43.3 mmol) in dry THF (216 ml), cooled at -20°C and under N_2 atmosphere, Et_3N (6.6 ml, 47.6 mmol) was added. After 15 min at -20°C, a solution of MsCl (3.7 ml, 47.6 mmol) in dry THF (130 ml) and Et_3N (13.2 ml, 95.2 mmol) were sequentially added. After stirring for 4 h, the white precipitate of Et_3N·HCl was filtered off, and the solvent was evaporated to give ***(S)-N*-allyloxycarbonylglutamic anhydride (5)**[8] as a yellow oil (quantitative). The crude product contained some Et_3N·HCl, but the anhydride was used without further purification due to its instability. ^1H NMR 2.26-2.36 (m, 2H, β-H), 2.91-2.94 (m, 2H, γ-H), 4.55-4.72 (m, 3H, OCH_2 and α-H), 5.20 (d, J = 10 Hz, 1H, CH=CH_A), 5.25, (d, J = 16 Hz, 1H, CH=CH_B), 5.80-5.95 (m, 1H, CH=CH_2); ^{13}C NMR 22.9 (C-β), 29.7 (C-γ), 50.8 (C-α), 66.0 (OCH_2), 117.9 (CH=CH_2), 132.3 (CH=CH_2), 156.0 (NHCOAlloc), 165.5 and 166.8 (CO anhydride).

A solution of anhydride **5** (8.8 g, 41.52 mmol) and di-*tert*-butyl-L-serine (3.9 g, 18.9 mmol) in dry $CHCl_3$ (400 ml) was refluxed for 24 h. The $CHCl_3$ was evaporated, AcCl (110 ml, 1.27 mol) was added, and the mixture was refluxed for 5 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (75 ml) and washed with H_2O. The organic extracts, dried and evaporated, yielded a yellow oil that was chromatographed (hexane:AcOEt, 1:1 to 1:9) to obtain *N*-acetylated di-*tert*-butylserine (700 mg, 15%) and pure imide **6** (3.5 g, 45%). $[\alpha]_D$ = -46.2 (c = 1.01, $CHCl_3$). mp 64-65°C (AcOEt). IR ($CHCl_3$) 3345 (NH), 1794, 1732 and 1689 (CO), 1535 (C=C); ^1H NMR 1.15 (s, 9H, $OC(CH_3)_3$), 1.47 (s, 9H, $CO_2C(CH_3)_3$), 2.20-2.30 (m, 2H, 4-H), 2.50 (ddd, J = 17, 8, and 4 Hz, 1H, 5-H_A), 2.78 (dt, J = 17 and 10 Hz, 1H, 5-H_B), 3.52 (dd, J = 9 and 3 Hz, 1H, β-H_A), 3.82 (dd, J = 9 and 3 Hz, 1H, β-H_B), 4.58-4.65 (m, 2H, 3-H and α-H), 4.73 (d, J = 8 Hz, 2H, OCH_2), 5.25 (d, J = 10 Hz, 1H, CH=CH_A), 5.40 (d, J = 10 Hz, 1H, CH=CH_B), 5.87-6.01 (m, 1H, CH=CH_2), 6.65 (d, J = 8 Hz, 1H, NH); ^{13}C NMR 22.3 (C-4), 27.5 ($OC(CH_3)_3$), 27.9 ($CO_2C(CH_3)_3$), 31.3

(C-5), 53.0 (C-α), 59.7 (C-3), 61.9 (C-β), 67.2 (OCH_2), 73.2 ($OC(CH_3)_3$), 82.0 ($CO_2C(CH_3)_3$), 118.7 ($CH=CH_2$), 131.2 ($CH=CH_2$), 151.2 (NHCOAlloc), 169.0 (C-2), 170.0 (C-6), 173.3 ($CO_2C(CH_3)_3$). CIMS *m/z* 413 (M^++1), 441 (M^++29), 453 (M^++41). Anal. Calcd for $C_{20}H_{32}N_2O_7$: C, 58.24; H, 7.82; N, 6.79. Found: C, 58.29; H, 7.86; N, 6.65.

Reduction of imide 6. Method A (7): To a solution of imide **6** (150 mg, 0.36 mmol) in dry THF (12 ml), at -20°C and under N_2 atmosphere, $NaBH_4$ (68 mg, 1.81 mmol) was added portionwise, and the mixture was stirred at the same temperature for 5 h. If tlc showed that there was still some starting material, $NaBH_4$ (68 mg, 1.81 mmol) was added and the reaction was stirred for 2 h more.The reaction was quenched by addition of saturated aqueous NH_4Cl. The solvent was evaporated and the residue, dissolved in CH_2Cl_2 (10 ml), was washed with saturated aqueous NH_4Cl (2 x 10 ml). The organic extracts, dried and evaporated, gave a yellow oil which was chromatographed (hexane:Et_2O, 1:1 to 3:7) to isolate hydroxyamide **7** (75 mg, 50%). $[\alpha]_D$ = +173.5 (c = 0.99, $CHCl_3$). IR ($CHCl_3$) 3400-3200 (OH), 1735 and 1657 (CO), 1530 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.15 (s, 9H, $OC(CH_3)_3$), 1.46 (s, 9H, $CO_2C(CH_3)_3$), 1.63-1.73 (m, 2H, 4-H), 1.86 (q, *J* = 7 Hz, 1H, 3-H_A), 1.95 (q, *J* = 7 Hz, 1H, 3-H_B), 3.52 (dd, *J* = 9 and 3 Hz, 1H, β-H_A), 3.60 (br s, 1H, OH), 3.65-3.74 (m, 2H, 5-H), 3.79 (dd, *J* = 9 and 3 Hz, 1H, β-H_B), 4.38 (dd, *J* = 14 and 6 Hz, 1H, 2-H), 4.54-4.64 (m, 3H, α-H and OCH_2), 5.20 (dd, *J* = 10 and 1 Hz, 1H, CH=CH_A), 5.30 (dd, *J* = 17 and 1 Hz, 1H, CH=CH_B), 5.80 (br d, *J* = 8 Hz, 1H, NH), 5.83-5.98 (m, 1H, C*H*=CH_2), 6.98 (br d, *J* = 8 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) 27.2 ($OC(CH_3)_3$), 27.8 (C-3), 27.9 ($CO_2C(CH_3)_3$), 30.2 (C-4), 53.1 (C-α), 54.1 (C-2), 61.9 (C-β), 62.1 (C-5), 65.7 (OCH_2), 73.1 ($OC(CH_3)_3$), 81.9 ($CO_2C(CH_3)_3$), 117.6 ($CH=CH_2$), 132.6 ($CH=CH_2$), 156.0 (NHCOAlloc), 169.2 (C-1), 171.3 ($CO_2C(CH_3)_3$). CIMS *m/z* 417 (M^++1), 445 (M^++29), 457 (M^++41). Anal. Calcd. for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.73. Found: C, 57.46; H, 8.86; N, 6.46.

Method B (7 and 8): To a solution of imide **6** (1 g, 2.42 mmol) in dry THF (12 ml), at -78°C and under N_2 atmosphere, DIBAH (7.28 ml, 7.28 mmol) was slowly added and the mixture was stirred for 1 h at this temperature. The reaction was quenched with saturated aqueous NH_4Cl. The solvent was evaporated, and the residue, dissolved in AcOEt (50 ml), was washed with saturated aqueous NH_4Cl (2 x 25 ml) and with brine. The organic extracts, dried and evaporated, gave a yellow oil which was chromatographed (hexane:Et_2O, 1:1 to 3:7 gradient) to yield a mixture of pure hydroxyamide **7** (lower Rf, 31%) and hydroxylactams **8a,b** (higher Rf, 39%, **a:b** = 2.3:1)

Method C (8): To a solution of imide **6** (1 g, 2.42 mmol) in dry THF (12 ml), cooled to -78°C and under N_2 atmosphere, $LiEt_3BH$ (6 ml, 6 mmol) was slowly added and the mixture was stirred for 2 h at the same temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and 30% H_2O_2 (2 ml) to destroy the excess hydride. The solvent was evaporated, and the residue was dissolved in Et_2O (50 ml) and washed with H_2O. The organic extracts, dried and evaporated, yielded hydroxylactams **8** as a yellow oil (40-50%): IR ($CHCl_3$) 3400-3200 (OH), 1750, 1716 and 1656 (CO), 1530 (C=C) cm^{-1}; ^1H NMR (from the diastereomeric mixture **a,b**) 1.14 (s, 9H, $OC(CH_3)_3$), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.90-2.05 (m, 1H, 5-H_A), 2.10-2.20 (m, 1H, 5-H_B), 2.15-2.30 (m, 1H, 4-H), 3.50-3.55 (m, 1H, β-H_A), 3.75-3.80 (m, 1H, β-H_B), 4.35 (br s, 1H, 3-H), 4.55-4.60 (m, 1H, α-H), 4.65 (br s, 2H, OCH_2), 5.15-5.30 (m, 2H, CH=CH_2), 5.60 and 5.70 (2 br s, 1 H each, 6-H), 5.80-6.00 (C*H*=CH_2), 6.95 and 7.20 (2 br s, 1H each, NH); ^{13}C NMR 27.3 ($OC(CH_3)_3$), 27.9 ($CO_2C(CH_3)_3$), 28.6 (C-4), 31.7 and 33.8 (C-5), 53.0 and 53.3 (C-α), 60.9 and 61.1 (C-3), 61.9 and 62.1 (C-β), 66.4 (OCH_2), 72.9 ($OC(CH_3)_3$), 81.6 and 82.4 ($CO_2C(CH_3)_3$), 83.2 (C-6), 117.7 and 117.9

(CH=CH_2), 132.3 (CH=CH_2), 154.5 (NHCOAlloc), 168.9 (C-2), 172.0 ($CO_2C(CH_3)_3$). CIMS *m/z* 415 (M^++1), 443 (M^++29), 455 (M^++41). Anal. Calcd for $C_{20}H_{34}N_2O_7$: C, 57.97; H, 8.21; N, 6.76. Found: C, 58.02; H, 8.43; N, 6.57.

(α*S*,3*RS*)-*N*-[2-*tert*-Butoxy-1-(*tert*-butoxycarbonyl)ethyl]-3-benzyloxycarbonyl-amino-Δ^5-piperidein-2-ones (11a,b). To a solution of di-*tert*-butyl serine·hydrochloride (183 mg, 0.72 mmol) and Et_3N (0.1 ml, 0.72 mmol) in dry C_6H_6 (2 ml), at 10°C and under N_2 atmosphere, a solution of aldehyde **9**[12] (200 mg, 0.72 mmol) in dry C_6H_6 (4 ml) was added. The mixture was refluxed for 48 h in a Dean-Stark trap. Once cold, the mixture was filtered and the solvent was evaporated. The resulting oil was a complex mixture from which enamides **11** (6%) were the only isolable product by column chromatography (hexane:Et_2O, 8:2 to 7:3), as a 1:4 C3 epimeric mixture. IR ($CHCl_3$) 3400 (NH), 1731 and 1678 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.16 and 1.28* (2s, $OC(CH_3)_3$), 1.45 and 1.58* (2s, $CO_2C(CH_3)_3$), 2.25 (tt, *J* = 15 and 3 Hz, 1H, 4-H_A), 2.32* (td, *J* = 15 and 7 Hz, 1H, 4-H_A), 2.84 (dt, *J* = 15 and 7 Hz, 4-H_B), 3.64 (dd, *J* = 10 and 3 Hz, 1H, β-H_A), 3.70* (br t, *J* = 6 Hz, 1H, β-H_A), 3.91 (dd, *J* = 10 and 6 Hz, 2H, β-H_B), 4.23* (m, 1H, 3-H), 4.34 (dt, *J* = 14 and 7 Hz, 1H, 3-H), 5.12 (br s, α-H and $CH_2C_6H_5$), 5.21 (br t, *J* = 6 Hz, 5-H), 5.79 (br d, *J* = 4 Hz, NH), 6.50 (dd, *J* = 8 and 3 Hz, 6-H), 7.35 (br s, C_6H_5); ^{13}C NMR ($CDCl_3$) 27.3 and 27.7* ($OC(CH_3)_3$), 27.8 and 27.9* ($CO_2C(CH_3)_3$), 29.3 (C-4), 50.9 (C-α), 56.9 (C-3), 61.4 (C-β), 66.8 ($CH_2C_6H_5$), 73.5 ($OC(CH_3)_3$), 82.2 ($CO_2C(CH_3)_3$), 104.2 (C-5), 128.0 (C_6H_5-*o*), 128.5 (C_6H_5-*m*), 129.1 (C_6H_5-*p* and C-6), 136.4 (C_6H_5-*i*), 168.3 (C-2), 179.0 (CO). EIMS *m/z* (%) 446 (M^+, 0.1), 373 (7), 317 (4), 96 (40), 57 (100).

4-Phenylthiocarbonyl-2-(*N*-phthaloyl)-*N*-[1-(*tert*-butoxycarbonyl)-2-*tert*-butoxyethyl]butanamides (13a,b). To a solution of thioester **12**[13] (500 mg, 1.35 mmol) in dry CH_2Cl_2 (7 ml) at 0°C and in N_2 atmosphere, HOBt (183 mg, 1.35 mmol) and DCC (335 mg, 1.62 mmol) were added at a 5 min interval. After 15 min, di-*tert*-butyl serine hydrochloride (343 mg, 1.35 mmol) and Et_3N (0.37 ml, 2.71 mmol) were added. The intense yellow suspension was stirred for 2 h at room temperature. The mixture was filtered, and washed with 1N HCl. The organic phase, dried and evaporated, gave a yellow oil which was chromatographed (hexane:AcOEt, 8:2 to 1:1) to yield amide **13** as a white foam (54%). IR ($CHCl_3$) 3300 (NH), 1790, 1720, 1686 and 1530 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 and 1.11 (s, 9H each, $OC(CH_3)_3$), 1.42 and 1.43 (2s, 9H each, $CO_2C(CH_3)_3$), 2.60-2.72 (m, 4H, 3-H), 2.73-2.82 (m, 4H, 4-H), 3.49 and 3.53 (2dd, *J* = 8 and 3 Hz, 1H each, β-H_A), 3.73 and 3.75 (2dd, *J* = 6 and 3 Hz, 1H each, β-H_B), 4.55 and 4.60 (2dt, *J* = 8 and 3 Hz, 1H each, α-H), 4.91 (br t, *J* = 8 Hz, 2H, 2-H), 6.73 and 6.85 (2br d, *J* = 8 Hz, 1H each, NH), 7.30-7.45 (m, C_6H_5), 7.72-7.80 (m, 4H, Pht-α), 7.85-7.92 (m, 4H, Pht-β); ^{13}C NMR ($CDCl_3$) 24.3 (C-3), 27.2 ($OC(CH_3)_3$), 27.8 ($CO_2C(CH_3)_3$), 40.0 (C-4), 52.9 (C-2), 53.5 (C-α), 61.8 (C-β), 72.8 and 72.9 ($OC(CH_3)_3$), 81.9 ($CO_2C(CH_3)_3$), 123.5 (Pht-α), 129.0 (C_6H_5-*o*), 129.3 (C_6H_5-*m* and -*p*), 132.2 (Pht-*quaternary*), 134.3 (Pht-β), 134.4 (C_6H_5-*i*), 167.3 and 167.4 (C-1), 167.6 and 167.7 ($CO_2C(CH_3)_3$), 195.9 and 196.0 (C-5). EIMS *m/z* (%) 568 (M^+,1), 495 (2), 459 (3), 403 (2), 329 (46), 301 (21), 186 (48), 57 (100). Anal. Calcd for $C_{30}H_{36}N_2O_7S$: C, 63.36; H, 6.38; N, 4.93; S, 5.64. Found: C, 63.29; H, 6.34; N, 4.91; S, 5.54.

* The star indicates the signals corresponding to the minor isomer.

4-Phenylthiocarbonyl-2-(*N*-phthaloyl)-*N*-[1-(methoxycarbonyl)-2-methylpropyl]butanamides (14a,b). To a solution of thioester **12** (1 g, 2.7 mmol) in dry DMF-CH_2Cl_2 (5:100) at room temperature, a solution of HOBt (0.43 g, 3.25 mmol) in dry DMF (5 ml) was added at room temperature. After 5 min DCC (0.82 g, 3.95 mmol) was added and the resulting yellow solution was stirred for 10 min before the addition of L-valine methyl ester (0.42 g, 3.2 mmol). The white suspension was stirred for 12 h at room temperature. The precipitated ureas were filtered off, the solvent was evaporated, and the residue was redissolved in Et_2O. The organic solution was washed with H_2O, citric acid (pH = 4), and 1N HCl, then dried and evaporated to give an oil which was chromatographed (hexane:AcOEt, 7:3) to obtain the amides **14** (54%), as a 1:1 epimeric mixture. IR ($CHCl_3$) 3376 (NH), 1777, 1718, 1696 and 1532 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 0.84 and 0.89 (2d, J = 7 Hz, γ-H), 2.15-2.19 (m, β-H), 2.61-2.68 (m, 3-H), 2.76 (t, J = 4 Hz, 4-H), 3.68 and 3.69 (2s, 3H each, CO_2CH_3), 4.50 and 4.53 (2dd, J = 5 and 3 Hz, 1H each, α-H), 4.85 (t, J = 7 Hz, 2-H), 6.60 (br d, J = 8 Hz, NH), 7.30-7.45 (m, C_6H_5), 7.72-7.80 (m, Pht-α), 7.85-7.92 (m, Pht-β); ^{13}C NMR ($CDCl_3$) 17.6 and 18.9 (C-γ), 24.5 (C-3), 31.1 (C-β), 40.0 (C-4), 52.2 (CO_2CH_3), 53.5 (C-2), 57.5 (C-α), 123.5 (Pht-α), 129.0 (C_6H_5-*o*), 129.3 (C_6H_5-*m* and -*p*), 132.2 (Pht-*quaternary*), 134.3 (Pht-β), 134.4 (C_6H_5-*i*), 168.0 (C-1), 172.0 (CO_2CH_3), 196.4 (C-5). EIMS *m/z* (%) 483 (M^++1, 0.1), 373 (24), 313 (100), 186 (71), 138 (61). Anal. Cald for $C_{25}H_{26}N_2O_6S$: C, 62.23; H, 5.43; N, 5.81; S, 6.65. Found: C, 62.08; H, 5.61; N, 5.88; S, 6.35.

4-Phenylthiocarbonyl-2-(*N*-phthaloyl)-*N*-[1-(methoxycarbonyl)-3-methylbutyl]butanamides (15a,b). Operating as above, from thioester **12** (1 g, 2.7 mmol), HOBt (0.36 g, 2.7 mmol), DCC (0.66 g, 3.24 mmol), and L-leucine methyl ester (0.32 g, 3.2 mmol) in DMF-CH_2Cl_2 (105 ml), compounds **15** (68%) were obtained, as a 1:1 epimeric mixture, after column chromatography (hexane:AcOEt, 7:3): IR ($CHCl_3$) 3369 (NH), 1776, 1719 and 1533 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 0.87-0.92 (m, δ-H), 1.48-1.67 (m, β-H and γ-H), 2.64-2.80 (m, 3-H and 4-H), 3.64 and 3.67 (2s, 3H each, CO_2CH_3), 4.57-4.67 (m, α-H), 4.82-4.96 (m, 2-H), 6.61 and 6.65 (2 d, J = 8 Hz, NH), 7.30-7.45 (m, C_6H_5), 7.72-7.80 (m, Pht-α), 7.85-7.92 (m, Pht-β); ^{13}C NMR ($CDCl_3$) 21.7 and 22.6 (C-δ), 24.5 (C-3), 24.7 (C-γ), 39.9 (C-β), 41.2 (C-4), 50.8 (C-2), 52.3 (CO_2CH_3), 53.2 (C-α), 123.5 (Pht-α), 129.0 (C_6H_5-*o*), 129.3 (C_6H_5-*m* and -*p*), 132.2 (Pht-*quaternary*), 134.3 (Pht-β), 134.4 (C_6H_5-*i*), 167.9 (C-1), 173.1 (CO_2CH_3), 196.4 (C-5). EIMS *m/z* 497 (M^++1, 0.1), 387 (12), 355 (20), 327 (65), 259 (28), 186 (100). Anal. Calcd for $C_{26}H_{28}N_2O_6S$: C, 62.89; H, 5.68; N, 5.64. Found: C, 62.62; H, 5.68; N, 5.69.

(α*S*,3*RS*)-*N*-[1-(*tert*-Butoxycarbonyl)-2-*tert*-butoxyethyl]-3-phthaloyl-Δ^5-piperidein-2-ones (19a,b). To a solution of amide **13** (1.3 g, 2.28 mmol) in dry CH_2Cl_2-CH_3CN (1:1, 23 ml), in the presence of 4Å molecular sieves and 10% Pd-C (130 mg) Et_3SiH (1.27 ml, 8.01 mmol) was slowly added. After 30 min, the reaction mixture was filtered and the solvent evaporated. The resulting aldehyde was dissolved in toluene (230 ml), *p*-TsOH (87 mg, 0.45 mmol) was added, and the mixture was refluxed in a Dean-Stark trap for 1 h. The reaction mixture was filtered, the solvent evaporated, and the resulting oil was chromatographed (hexane:AcOEt, 8:2) to obtain enamides **19a,b** as a white foam (1:1 epimeric mixture, 45%). IR ($CHCl_3$) 1780, 1750 and 1680 (CO), 1650 (C=C); ^1H NMR ($CDCl_3$) 1.19 (s, $OC(CH_3)_3$), 1.46 and 1.47* (2s, 9H each, $CO_2C(CH_3)_3$), 2.30-2.45 (m, 4-H_A), 3.29 and 3.37 (2tt, J = 16 and 2 Hz, 1H each, 4-H_B), 3.68 (dt, J = 10 and 3 Hz, β-H_A), 3.92 (dd, J = 10 and 6 Hz, β-H_B), 5.02 (dd, J = 6 and 3 Hz, α-H), 5.06-5.15 (m, 3-H), 5.15-5.23 (m, 5-H), 6.52 and 6.56 (2dd, J = 8 and 3 Hz, 6-H), 7.70-7.75 (m, Pht-α), 7.85-7.90 (m, Pht-β); ^{13}C NMR

($CDCl_3$) 24.1 and 24.2 (C-4), 27.2 and 27.3 ($OC(CH_3)_3$), 27.7 and 27.9 ($CO_2C(CH_3)_3$), 49.4 and 49.5 (C-3), 56.8 and 57.7 (C-α), 61.4 and 61.6 (C-β), 73.4 ($OC(CH_3)_3$), 82.0 ($CO_2C(CH_3)_3$), 102.7 and 102.8 (C-5), 123.5 (Pht-α), 129.5 and 129.9 (C-6), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.5 (Pht-CO), 167.7 (C-2). EIMS *m/z* (%) 442 (M^+, 2), 386 (4), 369 (2), 331 (8), 313 (13), 183 (17), 96 (43), 57 (100). Anal. calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.03; H, 6.97; N, 6.18.

(α*S*,3*RS*)-*N*-[1-(Methoxycarbonyl)-2-methylpropyl]-3-phthaloyl-Δ^5-piperidein-2-ones (20a,b). To a solution of amide **14** (700 mg, 1.45 mmol) in dry acetone (30 ml) and in the presence of 4Å molecular sieves and 10% Pd-C (60 mg), Et_3SiH (0.8 ml, 6.6 mmol) was slowly added. The resulting mixture was stirred at room temperature for 20 min, the solvent was evaporated, and the residue was dissolved in toluene (100 ml). *p*-TsOH (55 mg, 0.29 mmol) was added and the reaction was refluxed for 3 h. The reaction mixture was filtered, and the solvent evaporated to yield an oil, which was carefully chromatographed (hexane:AcOEt, 8:2) to afford the pure isomers of the enamides, as colorless oils. Enamide **(α*S*,3*S**)-20a** (lower Rf, 22%): $[\alpha]_D$ = -158 (c = 1.00, $CHCl_3$). IR ($CHCl_3$) 1779, 1720 and 1689 (CO), 1389 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 0.90 and 1.01 (2d, *J* = 6 Hz, 3H each, γ-H), 2.25-2.33 (m, 2H, β-H), 2.36 (ddd, *J* = 16, 8 and 7 Hz, 1H, 4-H_A), 3.25 (dddd, *J* = 16, 15, 3 and 2 Hz, 1H, 4-H_B), 3.76 (s, 3H, CO_2CH_3), 4.96 (d, *J* = 12 Hz, 1H, α-H), 5.09 (dd, *J* = 16 and 6 Hz, 1H, 3-H), 5.25 (ddd, *J* = 9, 7 and 2 Hz, 1H, 5-H), 6.34 (dd, *J* = 9 and 3 Hz, 1H, 6-H), 7.70-7.75 (m, 2H, Pht-α), 7.85-7.90 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 18.5 and 19.7 (C-γ), 24.5 (C-4), 28.7 (C-β), 49.2 (C-3), 52.2 (CO_2CH_3), 61.4 (C-α), 104.4 (C-5), 123.5 (Pht-α), 126.5 (C-6), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.5 (Pht-CO), 167.6 (C-2), 170.7 (CO_2CH_3). EIMS *m/z*: 357 (M^++1), 385 (M^++29), 398 (M^++41). Anal. Cald for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.62; N, 7.86. Found: C, 63.98; H, 5.87; N, 7.78. Enamide **(α*S*,3*R**)-20b** (higher Rf, 22%): $[\alpha]_D$ = + 34 (c = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) 1.00 and 1.02 (2d, *J* = 6 Hz, 3H each, γ-H), 2.15-2.27 (m, 2H, β-H), 2.41 (ddd, *J* = 16, 8 and 7 Hz, 1H, 4-H_A), 3.29 (dddd, *J* = 16, 15, 3 and 2 Hz, 1H, 4-H_B), 3.73 (s, 3H, CO_2CH_3), 4.96 (d, *J* = 10 Hz, 1H, α-H), 5.12 (dd, *J* = 15 and 7 Hz, 1H, 3-H), 5.32 (ddd, *J* = 9, 7 and 2 Hz, 1H, 5-H), 6.43 (dd, *J* = 9 and 3 Hz, 1H, 6-H), 7.70-7.75 (m, 2H, Pht-α), 7.85-7.90 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 18.4 and 19.4 (C-γ), 24.1 (C-4), 29.4 (C-β), 49.1 (C-3), 52.1 (CO_2CH_3), 60.5 (C-α), 105.2 (C-5), 123.5 (Pht-α), 126.6 (C-6), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.5 (Pht-CO), 167.6 (C-2), 171.0 (CO_2CH_3).

(α*S*,3*RS*)-*N*-[1-(Methoxycarbonyl)-3-methylbutyl]-3-phthaloyl-Δ^5-piperidein-2-ones (21a,b). Operating as above, from compound **15** (800 mg, 1.61 mmol), 4Å molecular sieves, 10% Pd-C (60 mg), Et_3SiH (0.8 ml, 6.6 mmol), in acetone (30 ml), and *p*-TsOH (60 mg, 0.3 mmol) in toluene (100 ml), an equimolar mixture of enamides **21a,b** was obtained, as a colorless oil. After repeated column chromatography (hexane:AcOEt, 8:2), diastereomers **21a** (32%) and **21b** (9%) were isolated pure, and a mixture fraction (39%, **a:b** = 1:3) was also obtained. Enamide **(α*S*,3*S**)-21a** (higher Rf): $[\alpha]_D$ = -96 (c = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.98 (d, *J* = 6 Hz, 6H, δ-H), 1.68-1.81 (m, 3H, β-H and γ-H), 2.41 (dt, *J* = 16 and 7 Hz, 1H, 4-H_A), 3.27 (tt, *J* = 16 and 3 Hz, 1H, 4-H_B), 3.72 (s, 3H, CO_2CH_3), 5.12 (dd, *J* = 15 and 7 Hz, 1H, 3-H), 5.32 (br t, *J* = 13 Hz, 1H, α-H), 5.29-5.37 (m, 1H, 5-H), 6.19 (dd, *J* = 8 and 3 Hz,1H, 6-H), 7.70-7.75 (m, 2H, Pht-α), 7.85-7.90 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 21.0 and 23.1 (C-δ), 24.1 (C-4), 24.6 (C-γ), 38.6 (C-β), 49.1 (C-3), 52.4 (CO_2CH_3), 53.1 (C-α), 105.3 (C-5), 123.4 (Pht-α), 126.5 (C-6), 131.9 (Pht-*quaternary*), 134.0 (Pht-β), 165.7 (Pht-CO), 167.5

(C-2), 171.7 (CO_2CH_3). EIMS *m/z* (%) 370 (M^+, 2), 339 (1), 311 (4), 223 (25), 167 (100). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.94; N, 7.56. Found: C, 64.50; H, 5.97; N, 7.36. Enamide **(α*S*,3*R**)-21b** (lower Rf): IR ($CHCl_3$) 1779, 1743 and 1686 (CO), 1350 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (d, *J* = 6 Hz, 6H, δ-H), 1.44-1.82 (m, 3H, β-H and γ-H), 2.36-2.50 (m, 1H, 4-H_A), 3.16-3.34 (m, 1H, 4-H_B), 3.74 (s, 3H, CO_2CH_3), 5.03-5.17 (m, 1H, 3-H), 5.24-5.36 (m, 2H, α-H and 5-H), 6.13-6.21 (m, 1H, 6-H), 7.71-7.77 (m, 2H, Pht-α), 7.85-7.88 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 21.3 and 22.3 (C-δ), 24.4 (C-4), 24.5 (C-γ), 37.9 (C-β), 48.9 (C-3), 52.2 (CO_2CH_3), 54.2 (C-α), 104.6 (C-5), 123.5 (Pht-α), 126.3 (C-6), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.5 (Pht-CO), 167.5 (C-2), 171.2 (CO_2CH_3).

(α*S*,3*RS*,5*RS*)-*N*-[1-(*tert*-Butoxycarbonyl)-2-*tert*-butoxyethyl]-3-phthaloyl-5-methylthiopiperidin-2-one (24a-d). To a solution of enamides **19a,b** (160 mg, 0.36 mmol), in dry THF (1.6 ml) cooled to -78°C, AIBN (catalytic amount) and CH_3SH (4 ml, 280 mmol), were added. The mixture was refluxed for 5 h. Once cooled (0°C), the reaction mixture was filtered and the solvent evaporated. The resulting foam was chromatographed (hexane:AcOEt, 8:2) to yield compounds **24a-d** (70%; *trans:cis* = 3:1) as a white solid. A sample of *trans*-**24** diastereomers was obtained by repeating the chromatography (**a** and **c**, higher Rf, 47%): IR ($CHCl_3$) 1790, 1727 and 1662 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.18 (s, $OC(CH_3)_3$), 1.45 (s, $CO_2C(CH_3)_3$), 2.15-2.20 (m, 4-H_A), 2.17 (s, SCH_3), 2.73 (ddd, *J* = 13, 10 and 6 Hz, 4-H_B), 3.36 (dt, *J* = 7 and 6 Hz, 5-H), 3.63-3.75 (m, 6-H_A i β-H_A), 3.86-3.95 (m, β-H_B), 4.00-4.15 (m, 6-H_B), 4.99 (dd, *J* = 6 and 3 Hz, α-H), 5.17 (dd, *J* = 10 and 8 Hz, 3-H), 7.62-7.65 (m, Pht-α), 7.75-7.80 (m, Pht-β); ^{13}C NMR ($CDCl_3$) 14.3 (SCH_3), 27.4 ($OC(CH_3)_3$), 27.9 ($CO_2C(CH_3)_3$), 30.5 (C-4), 39.3 (C-5), 47.0 (C-3), 50.7 (C-6), 58.3 (C-α), 61.4 (C-β), 73.3 ($OC(CH_3)_3$), 81.8 ($CO_2C(CH_3)_3$), 123.3 (Pht-α), 132.0 (Pht-*quaternary*), 133.9 (Pht-β), 165.4 (Pht-CO), 167.7 (C-2), 168.0 ($CO_2C(CH_3)_3$). Lactams *cis*-**24** (**b** and **d**, from a 3:1 *trans:cis* mixture): ^1H NMR ($CDCl_3$) 1.18 (s, $OC(CH_3)_3$), 1.46 (s, $CO_2C(CH_3)_3$), 2.17 (s, SCH_3), 2.15-2.20 (m, 4-H_A), 2.75-2.80 (m, 4-H_B), 3.35-3.41 (m, 5-H), 3.63-3.75 (m, 6-H_A i β-H_A), 3.86-3.95 (m, 2H, β-H_B), 4.00-4,15 (m, 6-H_B), 4.92 (dd, *J* = 6 and 3 Hz, α-H), 5.12 (dd, *J* = 10 and 8 Hz, 3-H), 7.62-7.65 (m, Pht-α), 7.75-7.80 (m, Pht-β); ^{13}C NMR ($CDCl_3$) 14.3 (SCH_3), 27.4 ($OC(CH_3)_3$), 27.9 ($CO_2C(CH_3)_3$), 30.5 (C-4), 39.3 (C-5), 47.1 (C-3), 50.6 (C-6), 58.8 (C-α), 61.4 (C-β), 73.3 ($OC(CH_3)_3$), 81.7 ($CO_2C(CH_3)_3$), 123.3 (Pht-α), 132.0 (Pht-*quaternary*), 133.9 (Pht-β), 166.5 (Pht-CO), 167.7 (C-2), 168.0 ($CO_2C(CH_3)_3$). EIMS *m/z* (%) 490 (M^+, 1), 361 (10), 313 (12), 291 (17), 246 (22), 57 (100). Anal. Calcd for $C_{25}H_{33}N_2O_6S$: C, 61.35; H, 6.74; N, 5.72; S, 6.54. Found: C, 61.31; H, 7.18; N, 5.59; S, 6.21.

(α*S*,3*S,5*RS*)-*N*-[1-(Methoxycarbonyl)-2-methylpropyl]-3-phthaloyl-5-methylthiopiperidin-2-ones (25).** To a solution of enamide **20a** (0.2 g, 0.56 mmol) in dry toluene (5 ml), AIBN (catalytic amount) and CH_3SH (excess) were added at 0°C. The reaction mixture was heated in a sealed tube at 80°C. The reaction was cooled to 0°C, and a tlc control was done every 5 h. If there was any starting enamide left, some more AIBN (catalytic amount) and more CH_3SH was added, and the reaction was continued (80°C). The excess CH_3SH and the toluene were evaporated to obtain a yellow oil that was flash chromatographed (hexane:AcOEt, 1:1) to yield a 3:1 mixture of methylthio derivatives *trans*-**25a** and *cis*-**25b** (80%) Lactam ***trans*-25a** (higher Rf, 60%): $[\alpha]_D$ = -107.2 (c = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.95 and 0.96 (2d, *J* = 7 Hz, 3H each, γ-H), 2.15-2.20 (m, 2H, 4-H_A and β-H), 2.18 (s, 3H, SCH_3), 2.69 (ddd, *J* = 13, 10 and 4 Hz, 1H, 4-

H_B), 3.29-3.33 (m, 1H, 5-H), 3.35 (dd, J = 12 and 3 Hz, 1H, 6-H_A), 3.74 (s, 3H, CO_2CH_3), 3.86 (dd, J = 12 and 3 Hz, 1H, 6-H_B), 4.80 (d, J = 10 Hz, 1H, α-H), 5.08 (dd, J = 10 and 8 Hz, 1H, 3-H), 7.70-7.77 (m, 2H, Pht-α), 7.82-7.88 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 14.6 (SCH_3), 18.9 and 19.6 (C-γ), 27.6 (C-β), 30.5 (C-4), 39.5 (C-5), 47.0 (C-3), 47.9 (C-6), 51.9 (CO_2CH_3), 61.7 (C-α), 123.4 (Pht-α), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.4 (Pht-CO), 167.6 (C-2), 171.0 (CO_2CH_3). EIMS *m/z* (%) 404 (M^+, 5), 357 (96), 345 (60), 297 (100), 246 (77). Lactam ***cis*-25b** (lower Rf, 20%) IR ($CHCl_3$) 1776, 1717 and 1681 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) (from a diastereomeric mixture **a:b**, 3:1) 0.95 and 0.96 (2d, J = 7 Hz, 3H each, γ-H), 2.15-2.25 (m, 2H, 4-H_A and β-H), 2.16 (s, 3H, SCH_3), 2.48 (q, J = 11 Hz, 1H, 4-H_B), 3.07 (tt, J = 11 and 3 Hz, 1H, 5-H), 3.33-3.45 (m, 1H, 6-H_A), 3.58 (dd, J = 12 and 3 Hz, 1H, 6-H_B), 3.78 (s, 3H, CO_2CH_3), 4.70 (d, J = 10 Hz, 1H, α-H), 5.08 (dd, J = 10 and 8 Hz, 1H, 3-H), 7.70-7.79 (m, 2H, Pht-α), 7.80-7.90 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 14.0 (SCH_3), 22.9 and 23.6 (C-γ), 28.8 (C-β), 30.3 (C-4), 38.6 (C-5), 46.9 (C-3), 47.9 (C-6), 51.9 (CO_2CH_3), 61.6 (C-α), 123.4 (Pht-α), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.4 (Pht-CO), 167.6 (C-2), 171.0 (CO_2CH_3).

(α*S*,3*S,5*RS*)-*N*-[1-(Methoxycarbonyl)-3-methylbutyl]-3-phthaloyl-5-methylthiopiperidin-2-ones (26).** Operating as above, from enamide **21a** (0.2 g, 0.54 mmol), CH_3SH (excess), and AIBN (catalytic amount), in dry toluene (5 ml), compounds **26** were obtained (95%), as a 3:1 C-5 epimeric mixture of lactams *trans*-**26a** and *cis*-**26b**. Pure samples were obtained by repeating the chromatography (hexane: AcOEt, 6:4). Lactam ***trans*-26a** (lower Rf, major isomer, 61%): $[\alpha]_D$ = -68.0 (c = 0.3, $CHCl_3$). IR ($CHCl_3$) 1774, 1720, 1717 and 1656 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 0.84 and 0.89 (2d, J = 7 Hz, 3H each, δ-H), 1.50-1.70 (m, 3H, β-H and γ-H), 2.13 (s, 3H, SCH_3), 2.12-2.24 (m, 1H, 4-H_A), 2.73 (ddd, J = 13, 10 and 5 Hz, 1H, 4-H_B), 3.26 (ddd, J = 12, 6 and 1 Hz, 1H, 6-H_A), 3.35-3.45 (m, 1H, 5-H), 3.69 (s, 3H, CO_2CH_3), 3.80 (dd, J = 12 and 4 Hz, 1H, 6-H_B), 5.08 (dd, J = 10 and 8 Hz, 1H, 3-H), 5.26 (t, J = 8 Hz, 1H, α-H), 7.65-7.70 (m, 2H, Pht-α), 7.75-7.80 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 14.6 (SCH_3), 21.4 and 23.1 (C-δ), 24.9 (C-γ), 30.7 (C-4), 37.4 (C-β), 39.6 (C-5), 46.9 (C-3), 47.6 (C-6), 52.4 (CO_2CH_3), 54.2 (C-α), 123.4 (Pht-α), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.4 (Pht-CO), 167.7 (C-2), 171.7 (CO_2CH_3). EIMS *m/z* (%) 418 (M^+, 4), 371 (M^+-SMe, 93), 359 (43), 311 (94), 246 (100), 167 (36). Lactam ***cis*-26b** (higher Rf, minor isomer, 20%): $[\alpha]_D$ = -58.9 (c = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.91 and 0.97 (2d, J = 7 Hz, 3H each, δ-H), 1.50-1.60 (m, 1H, γ-H), 1.63-1.86 (m, 2H, β-H), 2.19 (s, 3H, SCH_3), 2.28-2.42 (m, 1H, 4-H_A), 3.01-3.12 (m, 1H, 4-H_B), 3.46-3.52 (m, 2H, 6-H_A and 5-H), 3.66-3.76 (m, 1H, 6-H_B), 3.77 (s, 3H, CO_2CH_3), 4.88 (dd, J = 12 and 6 Hz, 1H, 3-H), 5.14 (dd, J = 10 and 4 Hz, 1H, α-H), 7.62-7.65 (m, 2H, Pht-α), 7.75-7.80 (m, 2H, Pht-β); ^{13}C NMR ($CDCl_3$) 14.2 (SCH_3), 21.3 and 23.3 (C-δ), 24.7 (C-γ), 32.6 (C-4), 36.6 (C-β), 38.6 (C-5), 48.6 (C-3), 49.2 (C-6), 52.3 (CO_2CH_3), 55.0 (C-α), 123.4 (Pht-α), 132.0 (Pht-*quaternary*), 134.0 (Pht-β), 165.4 (Pht-CO), 167.5 (C-2), 170.0 (CO_2CH_3). EIMS *m/z* (%) 418 (M^+, 4), 371 (M^+-SMe, 22), 359 (93), 311 (53), 246 (42), 167 (100).

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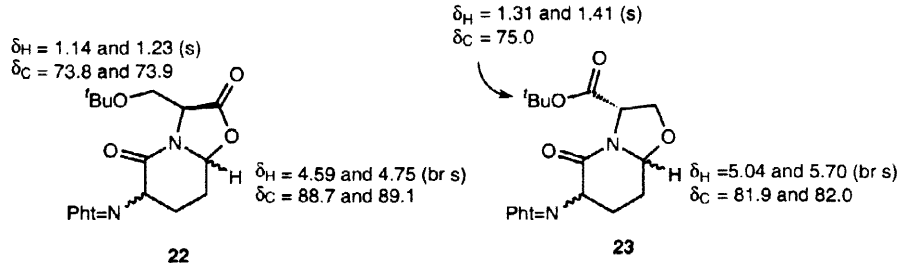
14. On one occasion enamides **19** (16%) were obtained together with oxazolidones **22** (29 %) and **23** (12 %), resulting from the loss of the *tert*-butyl protecting groups in the acid medium and cyclisation with the intermediate acyliminium salt. This explains the moderate yield of the reaction. In the absence of *p*-TsOH the reaction did not improve.



15. The absolute stereochemistry of the 3-position has not been determined. However, for the sake of clarity, we have called isomers **a** and **b** 3*S** and isomers **c** and **d** 3*R**.
16. This assignment was consistent with the major isomer observed in the phenylglycinol series,[4] whose stereochemistry has now been confirmed by X-ray crystallography.