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STEREOSELECTIVE SYNTHESIS OF UNNATURAL AMINOACIDS *CIS*-4-HYDROXYPROLINE AND BULGECININE

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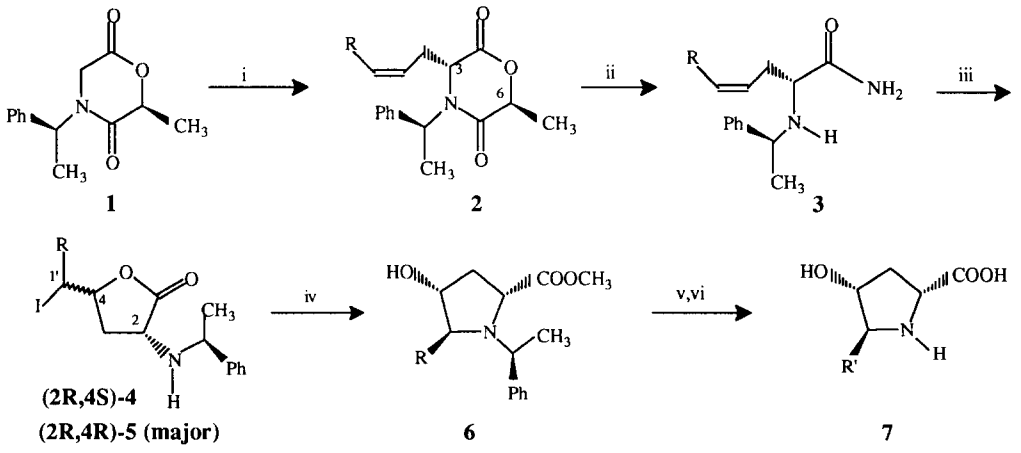
Abstract. A new stereoselective synthesis of both (2*R*,4*R*)- and (2*S*,4*S*)-4-hydroxy-proline and (+)- and (-)-bulgecinine was performed starting from synthons **1** or **1'**, respectively. The synthetic route has been established via a novel assisted cleavage of a disubstituted amide in mild conditions and successive stereocontrolled iodocyclization (Schemes 1 and 2).

In a recent paper[1] we have reported a new approach to the enantioselective synthesis of α-aminoacids through the highly stereocontrolled alkylation (a complete 1,4-*trans* induction was observed) of the chiral synthons (6*S*)-**1** and (6*R*)-**1'** 6-methyl-4-((1'S)-phenylethyl)-1,4-morpholine-2,5-diones. In a continuation of our studies directed towards the synthesis of optically active unnatural α-aminoacids, we accomplished an interesting use of synthons **1** and **1'** for the synthesis of optically active proline derivatives. We report here a new strategy for the synthesis of both (2*R*,4*R*)-(+)-**7a** and (2*S*,4*S*)-(-)-4-hydroxyproline-**7'a** and (+)-**7b** and (-)-bulgecinine-**7'b** (a proline derivative component of the antibiotic glycopeptide bulgecin). In the literature two stereospecific syntheses of bulgecinine[2] and an approach that makes use of a stereoselective cyclofunctionalization of the optically pure 2-amino-4-pentenoic acid[3] have been reported.



a) : R and R' = H ; b) : R = CH_2OBn and R' = CH_2OH

Scheme 1. i, 1M LHDMS,THF at -45°C, then (Z)-RCH=$CHCH_2X$; ii,NH_3/EtOH,at r.t.; iii,I_2 in THF/H_2O; iv,Na_2CO_3 in MeOH at r.t.; v,H_2/$Pd(OH)_2$ in MeOH; vi,1M NaOH in MeOH at r.t.

In Scheme 1 is reported the synthetic approach to (+)-*cis*-4-hydroxyproline **7a** and (+)-bulgecinine **7b**, starting from the synthon (6*S*)-**1**.

As we previously reported[1], the alkylation of synthon **1** occurs with total 1,4-*trans* induction and in good yield. The (3*R*) configuration of 1,4-morpholin-2,5-dione derivative **2** was assigned by the approach we already used for similar molecules[1,4]. Concerning the surprising conversion of lactone **2** into the amide **3**, under mild conditions, we investigated the reaction mechanism by performing suitable kinetic studies. The results, submitted for publication[5], evidenced that the cleavage of secondary amide arises from the intramolecular assistance of the neighbouring -$CONH_2$ group.

In agreement with the results obtained by Ohfune in the halocyclization of N-substituted 2-amino-4-pentenoic acids[3], the iodolactonization of amide **3** occurred with a relatively good *cis* selectivity affording the diastereomeric iodolactones **4a** and **5a** in 1:9 or **4b** and **5b** in 1:4 molar ratio, respectively[6]. The 2,4-*cis* relationship of iodolactones **5(a,b)** was determined by the n.O.e. experiments depicted in Figure 1. The configuration of stereogenic centre C-1' in **5b** is established as unequivocally correlated to that of C-4 : in fact, the iodocyclization is an *anti*-addition of amidic oxygen to the *Z*-double bond. So, it was possible to assign the absolute configuration (2*R*,4*R*) to iodolactone **5a** and (2*R*,4*R*,1'*R*) to **5b**.

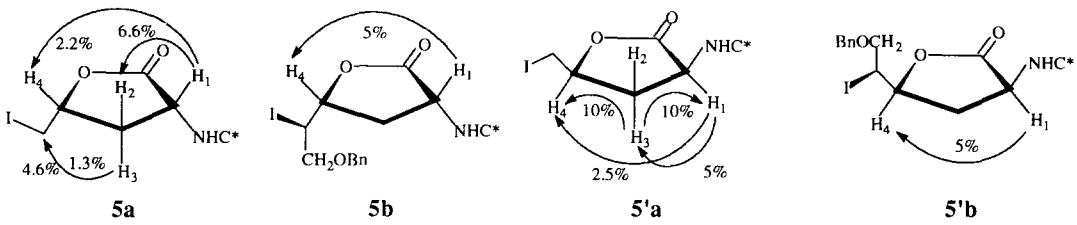
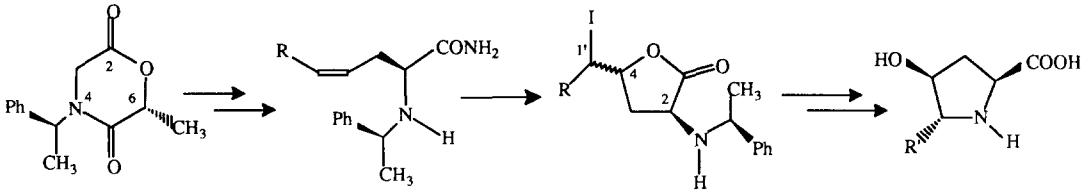


Figure 1. Where C* represents the (*S*)-phenylethyl chiral group.

The successive conversion, in alkaline medium, of iodolactone **5** into the N-substituted 4-hydroxy proline methyl ester **6** is, presumably, a sequential reaction promoted by the methoxy ion that opens the iodolactone allowing the successive intramolecular nucleophilic attack of nitrogen on C-1' which, in **5b**, induces the inversion of configuration. Because the iodolactones are not very stable, it is convenient to carry out the reaction directly on the crude product of the iodocyclization. Then the separation of diastereomers can be performed on the stable proline derivative **6**. The 2,4-*cis* configuration of **6(a,b)** was further confirmed by the presence of hydrogen bond between OH and $COOCH_3$ substituents : in fact, the proton of hydroxy group appeared as a doublet, at δ=3.65 ppm (J=7.2Hz) in **6a** and at δ=3.8 ppm (J=11.2Hz) in **6b**, and did not change upon varying the concentration of the substrates. Furthermore n.O.es were observed on (C-3)-H by irradiating both (C-2)-H and (C-4)-H confirming the *cis*-relationship.

Finally, the intermediate proline derivative **6** was easily converted into the final product **7** after hydrogenolysis on $Pd(OH)_2$ and successive alkaline hydrolysis of ester group.

The same reaction sequence carried out on the diastereomer (6R)-**1'** gave (-)-4-hydroxy proline (**7'a**) and (-)-bulgecinine (**7'b**) via iodocyclofunctionalization of (2*S*)-aminoester **3'(a,b)** to iodolactone **5'(a,b)** (Scheme 2). The relative configuration of intermediates **5'(a,b)** was assigned by n.O.e. measurements, in analogy to **5(a,b)**, as depicted in Figure 1. In this case, the ratios of *trans*-**4'(a,b)** and *cis*-**5'(a,b)** diastereomeric iodolactones were 1:4, respectively[6]. In the intramolecular cyclization of **5'b** to **6'b** was observed, as byproduct, ~15% of the epoxyester[7] deriving from the nucleophylic attack of carboxylic oxygen, instead of nitrogen, on the C-1'.



1' 3' (2S,4R)-4' (2S,4S)-5' (major) 7

Scheme 2. Where a) : R and R' = H ; b) : R = CH_2OBn and R' = CH_2OH.

By analogy to **6(a,b)**, the 2,4-*cis* configuration of **6'(a,b)** was further confirmed by the presence of hydrogen bond between OH and $COOCH_3$ substituents (see ^{1}H-NMR data in the experimental section) and by the n.O.e's observed on (C-3)-H by irradiating both (C-2)-H and (C-4)-H.

In conclusion, we have accomplished a simple method for synthesizing both (+)- and (-)-*cis* hydroxyproline and both the enantiomers of bulgecinine, the most salient features being the total 1,4-*trans* alkylation of synthon **1** or **1'**, the ammonolysis of diamide **2** or **2'** under very mild conditions and the stereocontrolled iodocyclization of the intermediate amide **3** or **3'**. Further investigations are in progress in order to employ both the chiral synthon **1** and **1'** in new approaches to the enantioselective synthesis of unnatural aminoacids.

Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Gemini-200 or 300 instruments using $CDCl_3$ as solvent, unless otherwise stated, and chemical shifts (δ) are related to tetramethylsilane. Optical rotation values were recorded on a Perkin Elmer 541 polarimeter. The reactions involving organometallic reagents were carried out under inert atmosphere in dry THF. Silica gel 60 (230-400 mesh) was employed for column chromatographic separations.

The starting synthon **1** and **1'** have been synthesized as previously reported[1].

(3*R*,6*S*,1'*S*)-4-(1'-Phenylethyl)-3-(2-propen-1-yl)-6-methyl-1,4-morpholin-2,5-dione 2a. It was prepared as previously described for similar substrates[1] by using iodoprop-2-ene, as alkylating reagent. After silica gel chromatography, the pure product was isolated in 90% yield as a solid (m.p.55-6°C); ^{1}H-NMR δ : 1.58 (d,3H,J=7.1Hz), 1.63 (d,3H,J=6.7Hz), 1.7 (ddd,1H,J=4.3, 7.4, 13.7Hz), 2 (ddd,11H,J=7.4, 9.5, 13.7Hz), 4.13 (dd,1H,J=4.3, 9.5Hz), 4.79 (m,1H), 5 (m,1H), 5.02 (q,1H,J=6.7Hz), 5.45 (m,1H), 5.95 (q,1H,J=7.1Hz), 7.4 (m,5ArH); ^{13}C-NMR δ : 15.8, 16.3, 36, 51.4, 55.8, 73.5, 119.7, 127.9, 128.4, 128.7, 130.8, 138.6, 165.9, 166.8; $[\alpha]_D$= -148.3 (c= 4.3, $CHCl_3$). Anal. calcd. for $C_{16}H_{19}NO_3$: C,70.31;H,7.01. Found : C,70.55;H,7.0.

(3*R*,6*S*,1'*S*)-4-(1'-Phenylethyl)-3-(4-benzyloxy-2(Z)-buten-1-yl)-6-methyl-1,4-morpholin-2,5-dione 2b. It was prepared as previously described for similar substrates[1] by using the appropriate methanesulfonate as alkylating reagent. After purification by silica gel chromatography, the product was isolated as an oil in 80% yield; ^{1}H-NMR δ : 1.54 (d,3H,J=7Hz), 1.56 (d,3H,J=7Hz), 1.7 (ddd,1H,J=4.6, 8.4, 14.1Hz), 2.1 (ddd,1H, J=7.7, 10.1, 14.1Hz), 3.69 (m,2H), 4.07 (dd,1H,J=4.6, 10.1Hz), 4.4 (q_{AB},2H,J=11.9Hz), 4.9 (q,1H,J=7Hz), 5.26 (m,1H), 5.63 (m,1H), 5.93 (q,1H,J=7Hz), 7.3 (m,10ArH); ^{13}C-NMR δ : 15.9, 16.3, 29.8, 51.4, 55.5, 65.2, 72.2, 73.6, 125.1, 127.6, 127.9, 128.3, 128.4, 128.5, 128.9, 130.4, 132.9, 138.6, 166.1, 166.8; $[\alpha]_D$=-245 (c=1.08, $CHCl_3$). Anal. calcd. for $C_{24}H_{27}NO_4$: C,73.26;H,6.92. Found : C,73.35;H,6.95.

(2*R*,4*S*)-2-(2-Propen-1-yl)-4-phenyl-3-azapentanamide 3a. A solution of **2** (1.32 g, 3 mmol) in 20 ml of ethanol was cooled at 0°C then NH_3 bubbled through the solution. After ~30 min., the reaction flask was

stopped and kept overnight at r.t.. After testing by TLC (with hexane/ethyl acetate 1:1 as eluent) the reaction was evaporated in vacuo and extracted with ethyl acetate. The organic phase was dried, evaporated in vacuo and submitted to chromatographic purification. The product was obtained as an oil in 90% yield and the (R)-lactamide was recovered from the aqueous solution. ^{1}H-NMR δ : 1.38 (d,3H,J=6.6Hz), 1.65 (bs,NH), 2.5 (m,2H), 3.15 (dd,1H,J=4.5, 7Hz), 3.8 (q,1H,J=6.6Hz), 5.15 (m,2H), 5.3 (bs,NH), 5.75 (m,1H), 7.15 (bs,NH), 7.3 (m,5ArH); ^{13}C-NMR δ : 23.6, 36.4, 56.7, 58.9, 119.1, 126.6, 127.2, 128.6, 134, 144.5, 177; $[\alpha]_D$= -3.7 (c= 2.0, $CHCl_3$). Anal. calcd. for $C_{13}H_{18}N_2O$: C,71.53;H,8.31. Found : C,71.45;H,8.34.

(2*R*,4*S*)-2-(4-Benzyloxy-2(*Z*)-buten-1-yl)-4-phenyl-3-azapentanamide 3b. It was obtained, in 95% yield, following the procedure previously described for **3a**. ^{1}H-NMR δ : 1.37 (d,3H,J=6.6Hz), 1.7 (bs,NH), 2.55 (m,2H), 3.15 (dd,1H,J=4.6, 6.7Hz), 3.8 (q,1H,J=6.6Hz), 4.05 (m,2H), 4.55 (s,2H), 5.3 (bs,NH), 5.7 (m,2H), 7.1 (bs,NH), 7.3 (m,10ArH); ^{13}C-NMR δ : 23.6, 34.8, 56.7, 58.9, 70.3, 72, 126.6, 127.2, 127.5, 127.6, 127.7, 128.4, 128.5, 129.1, 131, 138.1, 144.4, 176.8; $[\alpha]_D$= -11.7 (c=1.0, $CHCl_3$). Anal. calcd. for $C_{21}H_{26}N_2O_2$: C,74.53;H,7.74. Found : C,74.5;H,7.76.

(2*R*,4*R*)-2-N-((S)-1-Phenylethyl)-4-iodomethyl-γ-butyrolactone 5a. To 0.65 g (3 mmol) of **3a** dissolved in 40 ml of THF/H_2O (3:1) was added iodine (2 gr, 8 mmol) and the reaction mixture was stirred at r.t. monitoring by TLC (hexane/ethyl acetate 1:1). After 30 min. the reaction was quenched by $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic extract was evaporated in vacuo and the crude product was submitted to silica gel chromatography, eluting with hexane/ethyl acetate. The pure product was recovered as an oil in 80% yield. ^{1}H-NMR δ : 1.45 (d,3H,J=6.7Hz), 1.8 (ddd,1H,J=10.2, 11.3, 14.6Hz), 2.31 (bs,NH), 2.72 (ddd,1H,J=5.5, 8.3, 14.6Hz), 3.24 (dd,1H,J=7.8, 10.2Hz), 3.43 (dd,1H,J=4.9, 10.2Hz), 3.46 (dd,1H,J=8.3, 11.3Hz), 3.83 (q,1H,J=6.7Hz), 4.33 (m,1H), 7.3 (m,5ArH); ^{13}C-NMR δ : 5.6, 24.3, 37.6, 55.7, 56.6, 76.2, 126.4, 127.6, 128.9, 144, 176.

(2*R*,4*R*,1'*R*)-2-N-((S)-1-Phenylethyl)-4-(2benzyloxy-1'-iodo-1-ethyl-yl)-γ-butyrolactone 5b. The product was obtained in 72% yield, as previously reported for **5a**. ^{1}H-NMR δ : 1.45 (d,3H,J=6.7Hz), 2 (ddd,1H,J=9.3, 11.5, 12.2Hz), 2.5 (ddd,1H,J=5.6, 8.3, 12.2Hz), 3.5 (dd,1H,J=8.3, 11.5Hz), 3.8 (q,1H,J=6.7Hz), 3.85 (m,2H), 4.15 (ddd, 1H,J=3.3, 5.6, 9.3Hz), 4.25 (ddd,1H,J=3.3, 5.7, 8.1Hz), 4.55 (q_{AB},2H,J=11.8Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 24.2, 32.8, 36.5, 54.9, 56.1, 72.2, 73, 75.2, 126.2, 127.2, 127.5, 127.7, 128.2, 128.5, 137.2, 143.6, 175.6.

(2*R*,4*R*,1'*S*)-1-(1'-Phenylethyl)-4-hydroxy-proline methyl ester 6a. To a solution of **5a** (0.74 g, 2.15 mmol) in 20 ml of methanol was added 1 gr (6 mmol) of anhydrous Na_2CO_3. The reaction mixture was stirred at r.t. for 1 day monitoring by TLC (hexane/ethyl acetate 3:2). Then the solution was filtered off, evaporated under vacuum, water was added to the residue and extracted with ethyl acetate. The organic layer was dried, evaporated in vacuo and the residue submitted to silica gel chromatography eluting with hexane/ethyl acetate. The product was isolated pure as an oil in 90%yield. ^{1}H-NMR δ : 1.4 (d,3H,J=6.8Hz), 1.82 (ddd,1H,J=2, 2.3, 14Hz), 2.25 (ddd,1H,J=5.1, 10.4, 14Hz), 2.7 (dd,1H,J=3.6, 9.6Hz), 3.2 (dd,1H,J=2, 9.6Hz), 3.4 (dd,1H,J=2.3, 10.4Hz), 3.4 (s,3H), 3.65 (q,1H,J=6.8Hz), 3.65 (d,OH,J=7.2Hz), 4.25 (m,1H), 7.3 (m,5ArH); ^{13}C-NMR δ : 21.6, 38.9, 51.7, 60.1, 62.4, 63.2, 71, 127, 127.1, 127.6, 128, 143.9, 177. $[\alpha]_D$= 27.2 (c= 2.5, $CHCl_3$). Anal. calcd. for $C_{14}H_{19}NO_3$: C,67.45;H,7.68. Found : C,67.65;H,7.7.

(2*R*,4*R*,5*S*,1'*S*)-1-(1'-Phenylethyl)-4-hydroxy-5-benzyloxymethyl-proline methyl ester 6b. It was obtained in 95% yield following the same procedure employed for **6a**. ^{1}H-NMR δ : 1.45 (d,3H,J=6.7Hz), 1.75 (dd,1H,J=1.2, 14.4Hz), 2.45 (ddd,1H,J=5.4, 9.9, 14.4Hz), 3.13 (dd,1H,J=6.3, 9.9Hz), 3.3 (dd,1H,J=3.1, 9.9Hz), 3.41 (s,3H), 3.53 (m,1H), 3.65 (dd,1H,J=1.2, 9.9Hz), 3.8 (d,OH,J=11.2Hz), 3.9 (q,1H,J=6.7Hz), 4.18 (dd,1H,J=5.4, 11.2Hz), 4.4 (s,2H), 7.3 (m,10ArH); ^{13}C-NMR δ : 21.7, 37.7, 51.9, 58.8, 62.2, 69.1, 73.2, 75,

127.5, 127.6, 128.1, 128.2, 128.4, 138.1, 144.1, 177.9; $[\alpha]_D$= 16 (c= 0.96, $CHCl_3$). Anal. calcd. for $C_{22}H_{27}NO_4$: C,71.52;H,7.37. Found : C,71.7;H,7.4.

(2*R*,4*R*)-4-Hydroxy-proline 7a. 1 g of **6a** (4 mmol) dissolved in 10 ml of ethanol was submitted to hydrogenolysis at r.t. in the presence of $Pd(OH)_2$ (~0.5 g) under 36 psi of hydrogen and the reaction was monitored by TLC (eluting with hexane/ethyl acetate 3:7). After ~5 hours the catalyst was filtered off and the solution concentrated in vacuo: the reaction was practically quantitative and the ^{1}H-NMR spectrum was coherent with the expected compound. Thus, the crude reaction product was submitted to the alkaline hydrolysis by stirring for 2 hours with 10 ml of 1M NaOH. The solution was acidified with 1M HCl and evaporated in vacuo. The residue was dissolved in water and purified by adsorption on ion exchange resin Amberlist H-15. The resin was washed with distilled water then eluted with 5MNH_4OH to recover the pure product in 85% yield; ^{1}H-NMR (D_2O) δ : 2.22 (ddd,1H,J=1.6, 3.6, 14.2Hz), 2.45 (ddd,1H,J=4.5, 10.4, 14.2Hz), 3.38 (dd,1H,J=3.8, 12.4Hz), 3.42 (dd,1H,J=1, 12.4Hz), 4.17 (dd,1H,J=3.6, 10.4Hz), 4.55 (m,1H), 4.8 (s,2H,OH,NH); ^{13}C-NMR (D_2O) δ : 37.2, 53, 59.7, 69.2, 174.5; $[\alpha]_D$= 57 (c= 2, H_2O)[8].

(2*R*,4*R*,5*S*)-4-Hydroxy-5-hydroxymethyl-proline [(+)-bulgecinine] 7b. The product was obtained in 80% yield following the previous procedure used for **7a**; ^{1}H-NMR (D_2O) δ : 2.15 (ddd,1H,J=5, 6.6, 14Hz), 2.65 (ddd,1H,J=5.8, 9, 14Hz), 3.7-3.9 (m,3H), 4.2 (dd,1H,J=6.6, 9Hz), 4.4 (ddd,1H,J=4.2, 5, 5.8Hz); ^{13}C-NMR (D_2O) δ : 37.2, 58.8, 60.1, 67.6, 71.3, 174.4; $[\alpha]_D$= 12.5 (c= 0.7, H_2O), [lit. $[\alpha]_D$= 13 (c= 0.75, H_2O)][2].

(3*S*,6*R*,1'*S*)-4-(1'-Phenylethyl)-3-(2-propen-1-yl)-6-methyl-1,4-morpholin-2,5-dione 2'a. The product is a solid (m.p.59-60°C); ^{1}H-NMR δ : 1.65 (d,3H,J=7.1Hz), 1.68 (d,3H,J=6.8Hz), 2.65 (m,2H), 3.9 (dd,1H, J=6.6, 6.6Hz), 5.07 (q,1H, J=6.8Hz), 5.22 (m,2H), 5.77 (m,1H), 5.85 (q,1H,J=7.1Hz), 7.3 (m,5ArH); ^{13}C-NMR δ : 16.7, 17.6, 37.8, 52.5, 56.3, 73.7, 120.6, 127.2, 128.4, 128.9, 129.1, 130.9, 138.2, 166.6, 166.9; $[\alpha]_D$= 86.9 (c= 2.16, $CHCl_3$). Anal. calcd. for $C_{16}H_{19}NO_3$: C,70.31;H,7.01. Found : C,70.15;H,7.04.

(3*S*,6*R*,1'*S*)-4-(1'-Phenylethyl)-3-(4-benzyloxy-2(Z)-buten-1-yl)-6-methyl-1,4-morpholin-2,5-dione 2'b. ^{1}H-NMR δ : 1.58 (d,3H,J=7.1Hz), 1.6 (d,3H,J=6.8Hz), 2.7 (m,2H), 3.83 (dd,1H,J=5.6, 8.4Hz), 4.01 (d,2H,J= 6.2Hz), 4.5 (s,2H), 4.95 (q,1H,J=6.8Hz), 5.55 (m,1H), 5.8 (m,2H), 7.3 (m,10ArH); ^{13}C-NMR δ : 16.5, 17.3, 31.2, 52.3, 55.9, 65.3, 72.3, 73.5, 125.4, 127, 127.7, 128.1, 128.2, 128.3, 128.9, 130.6, 137.7, 138.1, 166.5, 166.7; $[\alpha]_D$= 83.8 (c=1.15, $CHCl_3$). Anal. calcd. for $C_{24}H_{27}NO_4$: C,73.26;H,6.92. Found : C,73.47; H,6.9.

(2*S*,4*S*)-2-(2-Propen-1-yl)-4-phenyl-3-azapentanamide 3'a. ^{1}H-NMR δ : 1.35 (d,3H,J=6.9Hz), 1.75 (bs, 1H,NH), 2.12 (m,1H), 2.45 (m,1H), 2.95 (dd,1H,J=4.3, 8.8Hz), 3.7 (q,1H,J=6.9Hz), 5.1 (m,2H), 5.5 (bs,1H,NH_2), 5.55 (m,1H), 7.15 (bs,1H,NH_2), 7.3 (m,5ArH); ^{13}C-NMR δ : 24, 38.1, 56.9, 59, 118.5, 126.3, 127.1, 128.4, 134.2, 144.3, 177.7; $[\alpha]_D$= -15.8 (c= 2.12, $CHCl_3$). Anal. calcd. for $C_{13}H_{18}N_2O$: C,71.53; H,8.31. Found : C,71.64;H,8.28.

(2*S*,4*S*)-2-(4-Benzyloxy-2(*Z*)-buten-1-yl)-4-phenyl-3-azapentanamide 3'b. ^{1}H-NMR δ : 1.35 (d,3H, J=6.7Hz), 2.39 (m,2H), 2.9 (dd,1H,J=5.7, 7.3Hz), 3.65 (q,1H,J=6.7Hz), 4 (m,2H), 4.48 (s,2H), 5.4 (m,1H), 5.7 (bs,1H), 5.8 (m,1H), 7.3 (m,10ArH); ^{13}C-NMR δ : 24.1, 31.8, 57, 59.3, 65.1, 72.4, 126.4, 127.1, 127.6, 127.8, 128.3, 128.4, 129.3, 129.5, 137.9, 144.5, 177.6; $[\alpha]_D$=8.06 (c=1.5, $CHCl_3$). Anal. calcd. for $C_{21}H_{26}N_2O_2$: C,74.53;H,7.74. Found : C,74.45;H,7.72.

(2*S*,4*S*)-2-N-((*S*)-1-Phenylethyl)-4-iodomethyl-γ-butyrolactone 5'a. ^{1}H-NMR δ : 1.57 (d,3H,J=6.8Hz), 1.87 (ddd,1H,J=10, 11.5, 13.2Hz), 2.42 (ddd,1H,J=5.4, 8.5, 13.2Hz), 2.6 (bs,NH), 3.25 (dd,1H,J=7.3, 10.2Hz), 3.37 (dd,1H,J=5.1, 10.2Hz), 3.62 (dd,1H,J=8.5, 11.5Hz), 4.3 (m,1H), 4.48 (q,1H,J=6.8Hz), 7.3 (m,5ArH); ^{13}C-NMR δ : 6, 24.6, 38.7, 57.2, 58.4, 75.8, 126.5, 127.5, 129, 145, 177.

(2*S*,4*S*,1'*S*)-2-N-((*S*)-1-Phenylethyl)-4-(2-benzyloxy-1'-iodo-et-1-yl)-γ-butyrolactone 5'b. ^{1}H-NMR δ : 1.4 (d,3H,J=6.7Hz), 1.8 (ddd,1H,J=10, 11.7, 12.5Hz), 2.1 (ddd,1H,J=5.5, 8.6, 12.5Hz), 3.5 (dd,1H,J=8.6,

11.7Hz), 3.8 (m,2H), 4.05 (ddd,1H,J=3.3, 5.5, 10Hz), 4.15 (ddd,1H,J=3.3, 6.3, 7.8Hz), 4.2 (q,1H,J=6.7Hz), 4.5 (q_{AB},2H,J=11.7Hz), 7.3 (m,10ArH); ^{13}C-NMR δ : 24.7, 33.2, 37.6, 56.4, 57.9, 72.4, 73.2, 74.9, 127, 127.4, 127.7, 127.9, 128.5, 137.3, 144.5, 176.6.

(2*S*,4*S*,1'*S*)-1-(1'-Phenylethyl)-4-hydroxy-proline methyl ester 6'a. ^{1}H-NMR δ : 1.36 (d,3H,J=6.6Hz), 1.9 (ddd,1H,J=2, 2.7, 14Hz), 2.28 (ddd,1H,J=5.4, 10.4, 14Hz), 2.63 (dd,1H,J=3.9, 9.9Hz), 2.92 (dd,1H,J=1.7, 9.9Hz), 3.35 (d,OH,J=11.4Hz), 3.44 (dd,1H,J=2.7, 10.4Hz), 3.7 (q,1H,J=6.6Hz), 3.73 (s,3H), 4.18 (m,1H), 7.3 (m,5ArH); ^{13}C-NMR δ : 21.9, 39.2, 51.9, 59.4, 60.9, 61.8, 70.4, 127, 127.2, 128.1, 143.1, 176.7; $[\alpha]_D$= -59.8 (c= 2.1, $CHCl_3$). Anal. calcd. for $C_{14}H_{19}NO_3$: C,67.45;H,7.68. Found : C,67.54;H,7.65.

(2*S*,4*S*,5*R*,1'*S*)-1-(1'-Phenylethyl)-4-hydroxy-5-benzyloxymethyl-proline methyl ester 6'b. ^{1}H-NMR δ : 1.3 (d,3H,J=6.6Hz), 1.81 (d,1H,J=14Hz), 2.6 (ddd,1H,J=4.8, 10.2, 14.1Hz), 3.26 (m,2H), 3.35 (m,1H), 3.68 (s,3H), 3.8 (d,1H,J=10.2Hz), 3.85 (d,OH,J=12Hz), 4 (q,1H,J=6.6Hz), 4.13 (dd,1H,J=4.8, 12Hz), 4.48 (q_{AB},2H,J=12.1Hz), 7.3 (m.10ArH); ^{13}C-NMR δ : 24.3, 38.2, 52.2, 58.7, 61.9, 68.7, 69.8, 73.2, 75.4, 127, 127.5, 127.6, 128.4, 138.2, 145.1, 178.7; $[\alpha]_D$= -48.4 (c= 0.3, $CHCl_3$). Anal. calcd. for $C_{22}H_{27}NO_4$: C,71.52;H,7.37. Found : C,71.49;H,7.34.

(2*S*,4*S*)-4-Hydroxy-proline 7'a. For ^{1}H-NMR and ^{13}C-NMR data see **7a**; $[\alpha]_D$= -58.5 (c= 2, H_2O)[8]

(2*S*,4*S*,5*R*)-4-Hydroxy-5-hydroxymethyl-proline [(-)-bulgecinine] 7'b. For ^{1}H-NMR and ^{13}C-NMR data see **7b**; $[\alpha]_D$= -12 (c= 0.7, H_2O), [lit. $[\alpha]_D$= -13 (c= 0.75, H_2O)][2].

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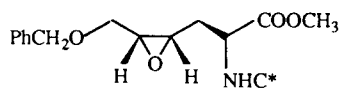
6. The diastereomeric ratios have been determined by ^{1}H-NMR.

7. Exclusively in the intramolecular cyclization of **5'b** to **6'b**, the formation of the epoxyester below (~15%) was observed. The product was characterized by ^{1}H-NMR spectrum :



8. The Merck Index, Eleventh Edition : $[\alpha]_D$= 58 (c= 2, H_2O) for the (4R)-4-hydroxy-(R)-proline and $[\alpha]_D$= -59 (c= 2, H_2O) for the (4S)-4-hydroxy-(S)-proline.

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