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AN IMPROVED PROCEDURE FOR THE ENANTIOSELECTIVE SYNTHESIS OF (+)- AND (-)-*CIS*-4-HYDROXYPROLINES AND BULGECININES

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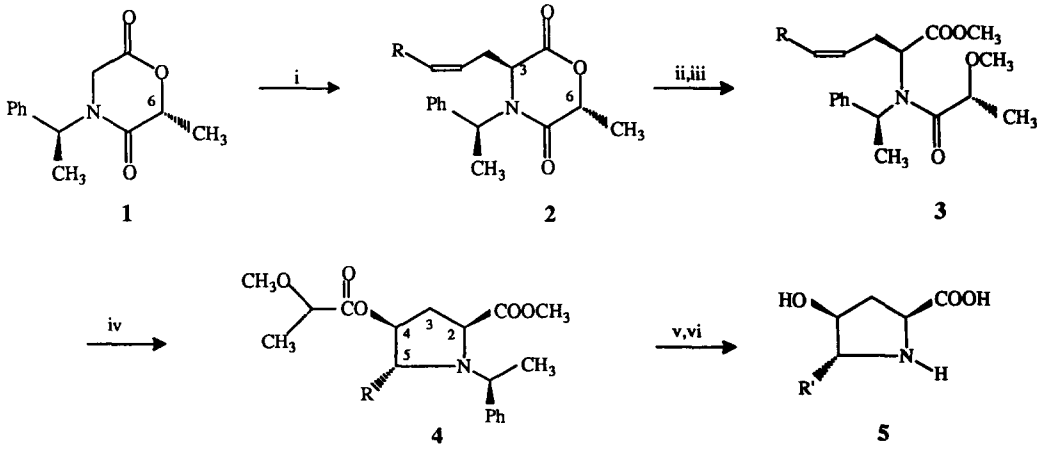
Abstract. An efficient enantioselective synthesis of both the enantiomers of *cis*-4-hydroxy-proline and bulgecinine was accomplished starting from synthons **1** or **1'**. The improved synthetic route to the aforesaid enantiomerically pure proline derivatives was established via a stereocontrolled double iodocyclization of **3(a,b)** or **3'(a,b)** Copyright © 1996 Elsevier Science Ltd

In a recent paper[1] we reported a new approach to the enantioselective synthesis of the unnatural aminoacids *cis*-4-hydroxyprolines (**5a** and **5'a**) and bulgecinines (**5b** and **5'b**) starting from the chiral synthons (6*S*)-**1** and (6*R*)-**1'** 6-methyl-4-N-((*S*)-1-phenylethyl)-1,4-morpholine-2,5-dione. As part of our investigations into the synthesis of optically active unnatural α-aminoacids, we investigated an interesting improvement of the previous procedure always starting from chiral synthons **1** and **1'**. This new synthetic approach makes use of a stereoselective double cyclofunctionalization of intermediate **3** to the 2,4-*cis*-proline derivative **4** (Scheme 1).



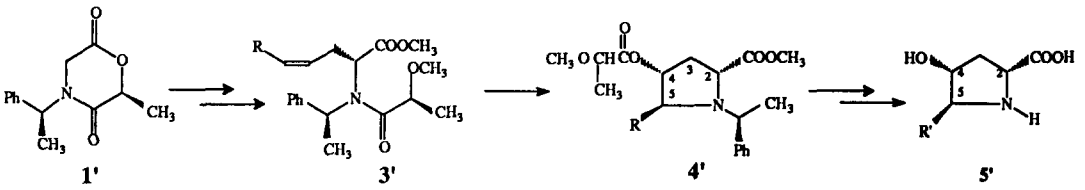
1 **2** **3** **4** **5**

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

Scheme 1. i, 1M LHDMS in THF at -40°C, then (*Z*)-$BnOCH_2CH{=}CHCH_2$-OMs (ref.1,2); ii, NaOH/MeOH; iii, NaH/THF at 0°C then CH_3I at 40°C; iv, I_2 in THF/H_2O; v, H_2/$Pd(OH)_2$ in MeOH; vi, 1M NaOH.

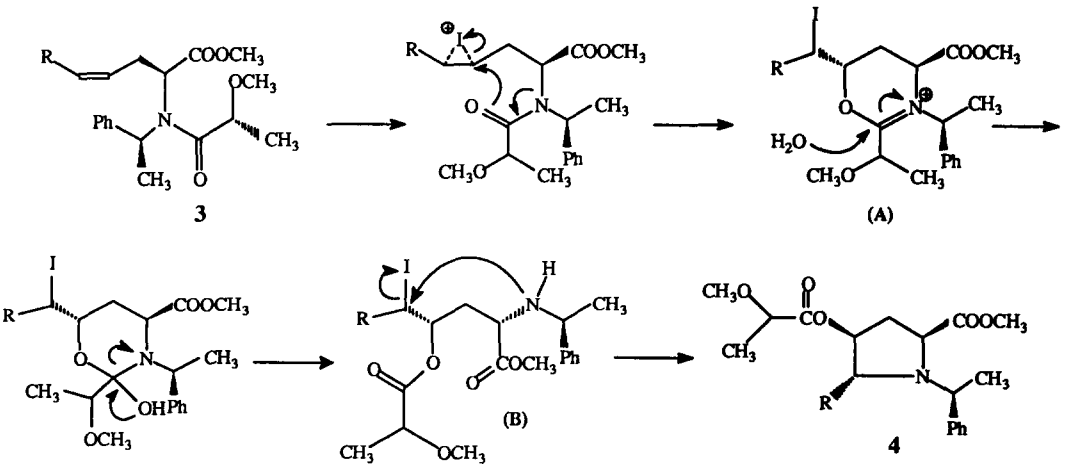
Scheme 1 shows the synthetic approach to the (-)-*cis*-4-hydroxyproline **5a** and (-)-bulgecinine **5b**, starting from the morpholine derivative **2** easily obtained from synthon (6*R*)-**1**[1,2].

The same reaction sequence carried out on the diastereomeric synthon (6*S*)-**1'** gave the (+)-*cis*-4-hydroxy proline **5'a** and (+)-bulgecinine **5'b** (Scheme 2).



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

The most salient features of this synthetic approach are the complete 1,4-*trans* alkylation[1,2] of **1** (or **1'**) and the highly stereocontrolled conversion of **3** (or **3'**) into **4** (or **4'**). Indeed, when R=H, the diastereomeric excesses[3] of 2,4-*cis* isomers **4a** and **4'a** were 82% and 88%, respectively, while when R=CH_2OBn exclusively the *cis* isomers **4b** and **4'b** were observed, although the iodocyclization was much slower. Indeed, while the formation of **4a** (or **4'a**) at r.t. was relatively fast (2 hours), about one week was necessary to convert **3b** (or **3'b**) into **4b** (or **4'b**) and monitoring of the reaction by TLC showed the formation of an intermediate which slowly afforded the final reaction product. This intermediate was isolated by silica gel chromatography and converted into the final product **4b** (or **4'b**) by heating for 20 hours at ~80°C in water/acetone 2:1. Spectroscopic data[4] led us to believe that the intermediate could be the aminodiester **B** proposed in the Scheme 3. In fact, as suggested in similar cases[5], the reaction should occur with a mechanism involving two consecutive cyclizations as reported in the following scheme :



Scheme 3. Mechanism proposed for the conversion of **3** into **4**.

The 1,3-*trans* stereoselection in the iodocyclization of **3** to the intermediate immonium ion **A** (Scheme 3) is in agreement with the results obtained by using a homoallylic carbamate when the amidic nitrogen is bonded to a

bulky substituent[6,7]. We suggest that the high asymmetric induction observed in our substrate **3** can be explained in terms of steric interactions in the transition-state, as shown in Figure 1. Indeed, owing to a strong steric repulsion between the bulky chiral auxiliary C* and the COOMe substituents, the **A** and **B** conformations appear energetically disfavoured with respect to **C** and **D**. Indeed, in the latter two a minor repulsive interaction is present because the carboxylic group is forced into a pseudo-axial position. On the other hand the **C** conformer is subject to a destabilizing steric interaction between R and COOMe substituents the extent of which is expected to be strongly dependent on both the stereochemistry of double bond and the bulkiness of R group. However, our assertions are consistent with the experimental results : indeed, if R=CH_2OBn complete stereoselection is observed, while with R=H less (82-88% d.e.) is observed. Lastly, the **D** conformation does not contain any remarkable steric interaction appearing to be the preferred conformer leading to the *trans* diastereomer of cyclic intermediate immonium ion **A** (proposed in Scheme 3). On the contrary, a reversal in diasteroselectivity has been observed if the amidic nitrogen is bonded to a small substituent[6]. Reasonably, this result can be attributed to the preferred formation of the thermodynamically more stable *cis* diastereomer since the contribution of conformer **A** to the conformational equilibrium becomes competitive with **D**.

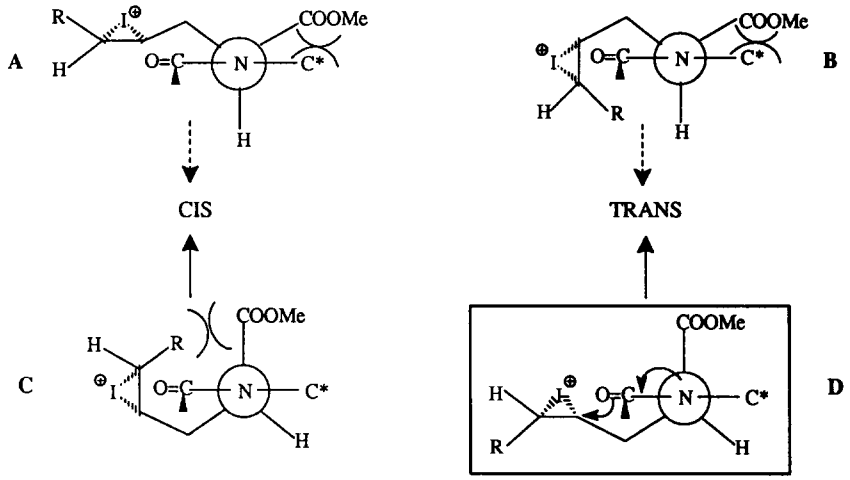


Figure 1. Possible conformers of the transition-state for the iodocyclization of **3** into the proposed cyclic intermediate immonium ion (see Scheme 3). The conformations are drawn by using the Newman projections along the (C-2)-N bond of **3** and C* represents the chiral (S)-phenylethyl group.

However, the mechanism proposed above to explain the stereochemical outcome of the conversion of **3** into **4** or **3'** into **4'** is coherent with the observed stereochemistry of the reaction products. The configuration of C-4 in **4** and **4'** was easily established being correlated to the stereocenter C-2 through (C-3)-H_b or (C-3)-H_c, respectively. Thus, the relative stereochemistry between C-2 and C-4 in **4a** was assigned by means of n.O.e. measurements : upon irradiation of both (C-2)-H_a (δ = 3.34 ppm) and (C-4)-H_d (δ = 5.2 ppm) n.O.e. was observed on the same hydrogen (C-3)-H_b (δ = 2.5 ppm), allowing us to attribute the 4*S* configuration to **4a**. Similarly, we established the 4*S* configuration in **4b** on the basis of the n.O.e. registered between (C-3)-H_b (δ = 2.75 ppm) and both (C-2)-H_a (δ = 3.88 ppm) and (C-4)-H_d (δ = 5.2 ppm) as shown in Figure 2 (see also Experimental Section).

In a similar manner, the configuration of C-4 both in **4'a** and **4'b** was established on the basis of the n.O.e. experiments depicted in Figure 2, the signals of H_a, H_c and H_d being at δ 3.68, 2.54, 5.22 ppm, respectively in **4'a**, and at δ 4.05, 2.55, 5.22 ppm, respectively in **4'b** (see Experimental Section).

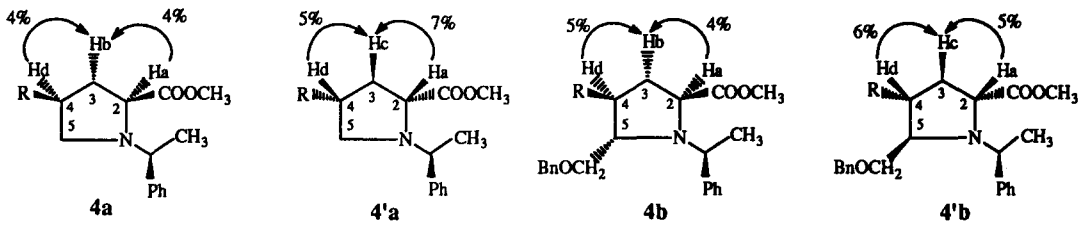


Figure 2. n.O.e.s registered on **4(a,b)** and **4'(a,b)** (R= $CH_3CH(OCH_3)$-COO-).

Lastly, the C-5 configuration in **4b** and in **4'b** is unequivocally determined because it is correlated to the C-4 stereocentre formed in the iodocyclization. In fact, this reaction is an *anti* addition of the amidic oxygen to the (*Z*)-double bond activated by iodine: thus, we assigned the absolute configuration *5R* to **4b** and *5S* to **4'b**.
Nevertheless, the absolute configurations previously attributed on the basis of ^{1}H-NMR data were unambiguously confirmed by comparison of the specific rotations in our products **5(a,b)** and **5'(a,b)** with those reported in the literature. The desired unnatural (-)- and (+)-*cis*-4-hydroxyprolines **5a** and **5'a** and both the enantiomers of bulgecinine **5b** and **5'b** were recovered in good yields after hydrogenolysis [H_2/$Pd(OH)_2$] of **4(a,b)** or **4'(a,b)**, respectively, and subsequent mild alkaline hydrolysis.
Therefore the described strategy, starting from the synthon **1**, or **1'**, proceeds in very good stereoselection enabling an efficient synthesis of the unnatural aminoacids *cis*-4-hydroxyproline and bulgecinine in both enantiomeric forms, which represents a good alternative to the synthetic approach previously reported[1].

Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Gemini-200 or 300 instruments using $CDCl_3$ as solvent 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 products **2a**, **2'a**, **2b** and **2'b** have been synthesized using the procedure previously given[1].
***(2S,5R,1'S)*-2(Propen-1-yl)-3-aza-(1'-phenylethyl)-4-oxa-5-methoxy-methyl hexanoate 3a.** In a stirred solution of **2a** (1.92 g, 7 mmol) in 10 ml of ethanol were dropped 7 ml of 1M NaOH. After 4 hours, the reaction was concentrated in vacuo and the sodium salt obtained was carefully dried then dissolved in 30 ml of dry THF. To the solution, stirred at 0°C under inert conditions, were added 0.27 g (7 mmol) of NaH (60% dispersion in mineral oil) and after ~2 hours 3.5 ml (56 mmol) of CH_3I. The reaction mixture was stirred overnight at r.t. then warmed at 60°C. After ~1 hour the reaction was cooled at r.t., added water and extracted with ethyl acetate. The organic layer was then dried and evaporated in vacuo. After silica gel chromatography the pure product was isolated as an oil in 90% yield. ^{1}H-NMR (δ) 1.48 (d,3H,J=6.8Hz), 1.66 (d,3H,J=7.1Hz), 2.45 (ddd,1H,J=4.6, 8.8, 14Hz), 3.2 (ddd,1H,J=7.7, 9.4, 14Hz), 3.4 (s,3H), 3.42 (ddd,1H,J=4.6, 7.7Hz), 3.49 (s,3H), 4.33 (q,1H,J=7.1Hz), 5.04 (m,,1H), 5.09 (m,1H), 5.47 (q,1H,J=6.8Hz), 5.9 (m,1H), 7.35 (m,5ArH); ^{13}C-NMR (δ) 16.8, 19.3, 35.8, 51.5, 54.5, 56.1, 56.8, 75.9, 116.6, 127.7, 128, 128.1, 135.9, 138.5, 170.4, 171.1; $[\alpha]_D$= -32.5 (c=2.15, $CHCl_3$)

(*2S,5R,1'S*)-2(Benzyloxy-2(*Z*)-buten-1-yl)-3-aza-(1'-phenylethyl)-4-oxa-5-methoxy-methyl hexanoate 3b. It was obtained following the same procedure given for **3a**; ^{1}H-NMR (δ) : 1.47 (d,3H,J=6.6Hz), 1.62 (d,3H,J= 7.1Hz), 2.45 (ddd,1H,J=4.7, 6.5, 14.8Hz), 3.3 (ddd,1H,J=6.4, 7.9, 14.8Hz), 3.35 (s,3H), 3.4 (dd,1H,J=4.7, 7.9Hz), 3.47 (s,3H), 4.12 (m,2H), 4.32 (q,1H,J=6.6Hz), 4.53 (s,2H), 5.45 (q,1H,J=7.1Hz), 4.53 (s,2H), 5.45 (q,1H,J=7.1Hz), 5.68 (m,2H), 7.3(m,10ArH); ^{13}C-NMR (δ) : 16.8, 19.3, 29.9, 51.7, 54.8, 56.4, 56.9, 66, 72.4, 76.1, 127.5, 127.6, 127.8, 128, 128.2, 128.3, 128.7, 130.1, 138.5, 170.4, 171.3; $[\alpha]_D$= -19.9 (c=2.26, $CHCl_3$).

(*4S,1'S*)-N-(1'-Phenylethyl)-4-O-(2-methoxy-propanoil)-(*S*)-proline methyl ester 4a. To 11.36 g (4.3 mmol) of intermediate **3a**, dissolved in 100 ml of THF/H_2O (4:1), were added g 3.17 (12.8 mmol) of iodine and the reaction mixture, monitored by TLC (eluting with hexane/ethyl acetate 6:4), was stirred at r.t. for 2 hours. Then the reaction was quenched by $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic solution was concentrated in vacuo and the crude product, consisting of *cis* and *trans* isomers in 9:1 ratio, respectively, was submitted to silica gel chromatographic purification. The pure product was isolated as an oil, in 80% yield. ^{1}H-NMR (δ) 1.35 (d,3H,J=6.9Hz), 1.4 (d,3H,J=6.9Hz), 2 (ddd,1H,J=2.8, 5, 14.1Hz), 2.5 (ddd,1H,J=7.4, 9, 14.1 Hz), 3.05 (m,2H), 3.34 (dd,1H,J=5, 9Hz), 3.38 (s,3H), 3.7 (s,3H), 3.87 (q,1H,J=6.9Hz), 3.92 (q,1H,J=6.9 Hz), 5.2 (m,1H), 7.3 (m,5ArH); ^{13}C-NMR (δ) 18.2, 21.8, 36.5, 51.7, 55.4, 57.6, 60.7, 61.3, 72.9, 76, 127.4, 128.3, 128.4, 1172.9, 174; $[\alpha]_D$= -59.4 (c= 2.32, $CHCl_3$).

(*4S,5R,1'S*)-N-(1'-Phenylethyl)-4-O-(2-methoxy-propanoil)-5-(benzyloxymethyl)-(*S*)-proline methyl ester 4b. A mixture of **3b** and iodine in THF/H_2O (as described for **4a**) was stirred at r.t. for one week. After silica gel chromatography the pure product was isolated in 70% yield. ^{1}NMR (δ) 1.28 (d,3H,J=6.8Hz), 1.4 (d,3H, J=6.5Hz), 1.95 (dd,1H,J=2.7, 14.8Hz), 2.75 (ddd,1H,J= 5.8, 10.2, 14.8Hz), 3.4 (s,3H), 3.45 (m,3H), 3.65 (s,3H), 3.88 (dd,1H,J=2.7, 10.2Hz), 3.9 (q,1H,J= 6.8Hz), 4.48 (qAB,2H,J=12.1Hz), 5.2 (d,1H,J=5.8Hz), 7.3 (m,10ArH); ^{13}C-NMR (δ) : 18, 23.9, 36.5, 51.4, 57.6, 58, 62.1, 65.5, 69.4, 73.2, 76.1, 78.2, 126.7, 126.8, 127, 127.1, 127.6, 127.7, 128.2; $[\alpha]_D$= -7.24 (c=2.0, $CHCl_3$).

(*4S*)-4-hydroxy-(*S*)-proline 5a. 1.06 g (3.16 mmol) of **4a** in 10 ml of methanol were submitted to hydrogenolysis in the presence of $Pd(OH)_2$ (0.3 g) under 36 psi of hydrogen at r.t. 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. As evidentied by TLC, the reaction was practically quantitative and both the I.R. and the ^{1}H-NMR spectra were coherent with the expected compound. To the crude product, dissolved in 10 ml of methanol, were added 10 ml of 1M NaOH and the mixture was stirred at r.t. for 2 hours. Then the solution was acidified with 1M HCl and evaporated under vacuum. The crude product was dissolved in 10 ml of water and purified by adsorption on ion exchange resin Amberlist H-15. The resin was washed with distilled water and then eluted with 5M NH_4OH to recover the pure product in 90% yield. The ^{1}H-NMR, ^{13}C-NMR spectra and specific rotation value are according to those previously reported[1].

(*4S,5R*)-4-Hdroxy-5-hydroxymethyl-(*S*)-proline [(-)-bulgecinine] 5b. It was obtained following the procedure used for **5a**: the^{1}H-NMR, ^{13}C-NMR spectra and specific rotation value are according to those previously reported[1].

(*2R,5S,1'S*)-2(Propen-1-yl)-3-aza-(1'-phenylethyl)-4-oxa-5-methoxy-methyl hexanoate 3'a. ^{1}H-NMR (δ) 1.67 (d,3H,J=7Hz), 1.7 (ddd,1H,J=3.7, 7.9, 13.7Hz), 2.84 (ddd,1H,J=6.2, 8.7, 13.7Hz), 3.4 (dd,1H,J=3.7, 8.7 Hz), 3.45 (s,3H), 3.7 (s,3H), 4.4 (q,1H,J=7Hz), 4.42 (m,1H), 4.65 (m,1H), 5.3 (m,1H), 5.5 (q,1H,J=6.6Hz), 7.4 (m,5ArH); ^{13}C-NMR (δ) : 16.7, 17, 35.3, 52.1, 54.4, 56.3, 57.4, 75.5, 1116.3, 128.1, 128.6, 135.6, 139.1, 170.6, 171.5; $[\alpha]_D$= -36.6 (c= 2.06, $CHCl_3$).

(*2R,5S,1'S*)-2(4-Benzyloxy-2(*Z*)-butenyl)-3-aza-(1'-phenylethyl)-4-oxa-5-methoxy-methyl hexanoate 3'b. ^{1}H-NMR (δ) : 1.5 (d,3H,J=6.6Hz), 1.65 (d,3H,J=7Hz), 1.82 (ddd,1H,J=3.8, 8, 15Hz), 2.98 (ddd,1H,J=7.5, 9,

15Hz), 3.4 (dd,1H,J=3.8, 9Hz), 3.45 (s,3H), 3.68 (s,3H), 3.71 (m,2H), 4.32 (s,2H), 4.37 (q,1H,J=7Hz), 4.85 (m,1H), 5.3 (m,1H), 5.5 (q,1H,J=6.6Hz), 7.3 (m,10ArH); ^{13}C-NMR (δ) : 16.6, 17.1, 29.5, 52.1, 54.4, 56.3, 56.8, 65.8, 72, 75.5, 127.4, 127.6, 127.7, 128, 128.3, 128.7, 129.3, 139.1, 170.8, 171.3; $[\alpha]_D$= -35.16 (c=5.76, $CHCl_3$).

(*4R,5S,1'S*)-N-(1'-Phenylethyl)-4-O-(2-methoxypropion-1-yl)-(*R*)-proline methyl ester 4'a. ^{1}H-NMR (δ) 1.32 (d,3H,J=6.9Hz), 1.38 (d,3H,J=6.9Hz), 2.04 (ddd,1H,J=2.6, 4.2, 14.3Hz), 2.54 (ddd,1H,J=7.4, 9, 14.3 Hz), 2.96 (dd,1H,J=6.1, 11Hz), 3.06 (dd,1H,J=2.8, 11Hz), 3.35 (s,3H), 3.56 (s,3H), 3.68 (dd,1H,J=4.2, 9Hz), 3.85 (2q,2H,J=6.9Hz), 5.22 (m,1H), 7.3 (m,5ArH); ^{13}C-NMR (δ) : 18.1, 20.7, 36.7, 51.3, 56.2, 57.5, 61.1, 61.5, 73, 75.9, 76.6, 127.1, 127.4, 128.1, 143.6, 172.8, 174; $[\alpha]_D$= -30.5 (c=1.16, $CHCl_3$).

(*4R,5S,1'S*)-N-(1'-Phenylethyl)-4-O-(2-methoxypropionyl)-5-(benzyloxymethyl)-(*R*)-proline methyl ester 4'b. ^{1}H-NMR (δ) : 1.35 (d,3H,J=6.9Hz), 1.35 (d,3H,J=6.6Hz), 1.95 (dd,1H,J=1.5, 14.5Hz), 2.55 (ddd,1H, J=6.1, 9, 14.5Hz), 2.82 (dd,1H,J=5.1, 9.8Hz), 3.1 (dd,1H,J=2.8, 9.8Hz), 3.38 (s,3H), 3.6 (s,3H), 3.85 (q,1H, J=6.9Hz), 4.05 (dd,1H,J=1.5, 9Hz), 3.46 (dd,1H,J=2, 5.1Hz), 4.2 (qAB,2H,J=12Hz), 4.25 (q,1H,J=6.6Hz), 5.22 (d,1H,J=6.4Hz), 7.3 (m,10ArH); ^{13}C-NMR (δ) : 18, 22, 36, 51.2, 57.5, 58.5, 62, 67.3, 69.6, 72.8, 76, 78.1, 127.1, 127.3, 127.6, 128, 128.1, 138.1, 145.3, 172.6, 174.9; $[\alpha]_D$= -44.1 (c=1.2, $CHCl_3$).

(*4R*)-4-Hdroxy-(*R*)-proline 5'a. See the procedure followed for **5a.** The ^{1}H-NMR, ^{13}C-NMR spectra and specific rotation value are according to those previously reported[1].

(*4R,5S*)-4-Hdroxy-5-hydroxymethyl-(*R*)-proline [(+)-bulgecinine] 5'b. See the procedure given for **5b.** The ^{1}H-NMR, ^{13}C-NMR spectra and specific rotation value are according to those previously reported[1].

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References and Notes

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3. The diastereomeric ratios were determined by ^{1}H-NMR.
4. The nature of the intermediate **B** is supported by the following experimental evidences. ^{1}H-NMR (δ) : 1.1 (d,3H,J=6.8Hz), 1.32 (d,3H,J=6.6Hz), 1.75-2.05 (m,2H), 2.96 (dd,1H,J=3.4, 10.3Hz), 3.16 (s,3H), 3.65 (m, 4H), 3.72 (s,3H), 4.48 (dt,1H,J=2.5, 6.8Hz), 4.53 (s,2H), 5.05 (ddd,1H,J=2.5, 4, 8.1Hz), 7.2-7.4 (m,10 ArH). ^{13}C-NMR (δ) 18.1, 25.3, 34.2, 38.1, 51.9, 55.5, 56.3, 57.6, 70.5, 72.5, 73, 76.2, 127, 127.1, 127.7, 128.4, 128.5, 137.6, 144.2, 171.8, 175.5. By irradiating the (C-2)-H at δ=2.96 ppm significant n.O.e. (5% and 1.5%) have been registered on both (C-4)-H (δ=5.05 ppm) and (C-5)-H (δ=4.48 ppm), respectively. Since no n.O.e. between (C-2)-H and (C-4)-H should be observed in a *trans* cyclic structure (as those hypotesized for the precursors of **B**), we are attempting to assign an open structure to the isolated intermediate. Besides, what is more, such intermediate, treated with acetyl chloride in triethylamine, gave a product whose IR spectrum shown a band at 1640 cm^{-1}, typical of a secondary amide.
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