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AN EFFICIENT STRAIGHTFORWARD SYNTHESIS OF (-)-BULGECININE

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Abstract. (-)-Bulgecinine **1**, a component of the antibiotic bulgecins, was efficiently synthesized from (*S*)-pyroglutaminol **2**.

An unnatural aminoacid (-)-bulgecinine **1** is the common constituent of *O*-sulfonated glycopeptides bulgecins found in the culture broth of *Pseudomonas acidophila*, *Pseudomonas mesoacidophila*[1] and *Chromobacterium violaceum*.[2] These natural products induce bulge formation in the cell wall of Gram-negative bacteria and are potent ß-lactam synergists. The unique biological activities associated with these bulgecins has been the subject of extensive studies in various research laboratories. Consequently, the synthesis of their non-proteinogenic aminoacid constituent has received much attention in recent years.[3-9] Particularly, (-)-bulgecinine **1** has been synthesized from chiral pool.[3-6] One of these syntheses was developed from (*S*)-pyroglutamic acid. It involved

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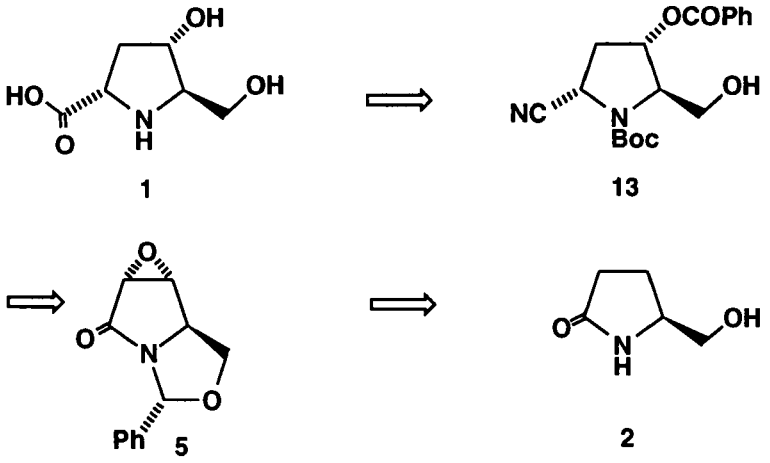
ring opening of *N*-Boc pyroglutamate with vinyl magnesium bromide, reduction of the carbonyl group and cyclization of the derived mesylate. Ozonolysis of the introduced vinyl group followed by reduction led to the hydroxymethyl group of bulgecinine **1**.[5]

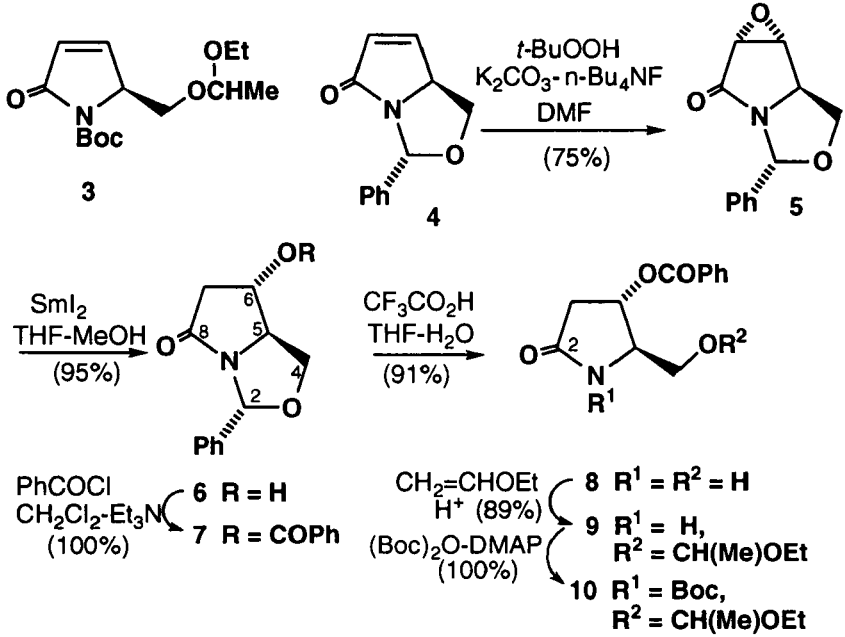
In our ongoing programme on the use of (*S*)-pyroglutaminol **2** as a chiral starting material,[10-15] we describe here an efficient and straightforward synthesis of **1** from **2** which already includes the required hydroxymethyl group as outlined in general scheme 1.

In connection with our previous studies, an oxirane was used as precursor of the secondary alcohol function and a cyano group was diastereoselectively introduced in the penultimate step as precursor of the carboxylic group.

As several trials to epoxidize directly *N*-alkoxycarbonyl-α,ß-unsaturated pyrrolidin-2-one (as **3**) failed,[16,17] we started with the well known γ-lactam **4** easily derived from (*S*)-pyroglutaminol (Scheme 2).[18] Diastereospecific epoxidation of **4** in DMF with *tert*-butylhydroperoxide in the presence of K_2CO_3 and tetrabutylammonium fluoride, as described by C. Herdeis and coll.,[19] gave rise to **5** in 75% yield. Efficient cleavage of the oxirane was performed by treatment with SmI_2 in a mixture THF-MeOH.[20] The resulting alcohol **6** obtained in 95% yield was quantitatively converted into its benzoate **7** (PhCOCl, 1.2 equiv., CH_2Cl_2-Et_3N). Controlled acidic hydrolysis of the oxazolidine ring of **7** with trifluoroacetic acid afforded the primary alcohol **8** (91%), which was *O*-protected as acetal (**9**) with ethyl vinyl ether before *N*-Boc protection to give **10** (100%). The crude compound **10** could be advantageously used without chromatographic purification (particularly on large scale), in order to preclude an easy ß-elimination leading to some amounts of the corresponding α,ß-unsaturated pyrrolidin-2-one **3** (Scheme 2).



Scheme 1



Scheme 2

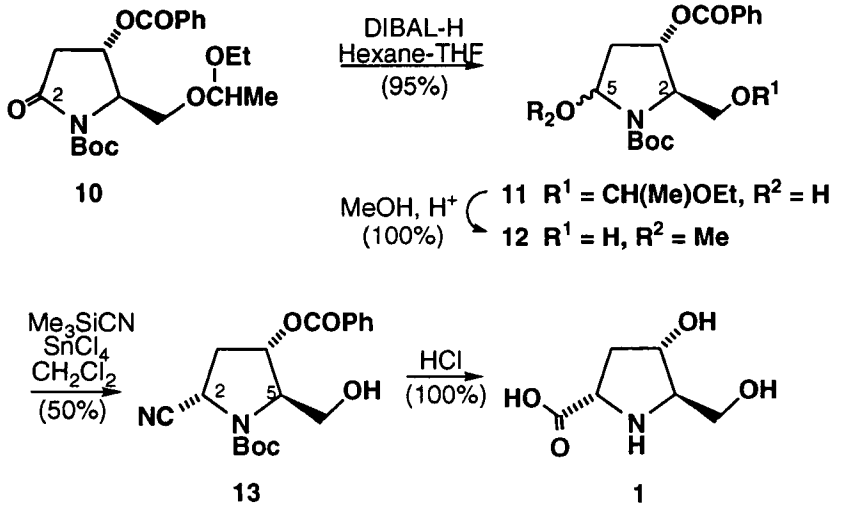
α-Methoxycarbamates **12** were prepared as a mixture of diastereomers (**12a** : **12b** = 72:28) by selective partial reduction of the γ-lactam carbonyl of **10** with DIBAL-H, followed by treatment with MeOH-TsOH (95%).

Taking advantage of our previous work in this field,[13,15] nucleophilic addition of cyanide to the α-methoxycarbamates **12** was anticipated to give stereoselectively the *trans* 2,5-disubstituted derivative, owing to the presence of the hydroxymethyl group at C-2. Thus, treatment of **12** with trimethyl silylcyanide in the presence of $SnCl_4$ at -40°C afforded, along with some unreacted **12a**, a mixture of two major components. The less polar compound was shown to be silylated by ^1H NMR; it was unstable and changed on standing into the more polar one, **13**, which was isolated in 50% overall yield (Scheme 3). The 2*S* configuration of the cyano derivative **13** was confirmed by its conversion into the target (-)-bulgecinine **1**. Accordingly, hydrolysis of nitrile **13** with 6N HCl allowed the deprotections of nitrogen and secondary alcohol in one quantitative step. (-)-Bulgecinine **1** was obtained in this way after treatment with propylene oxide.

Thus, following this simple synthetic scheme, (-)-bulgecinine **1** was synthesized from (*S*)-pyroglutaminol in 18% overall yield.

Experimental section

Optical rotations were measured on a Perkin-Elmer 241 ; the concentrations in $CHCl_3$ solution (unless otherwise indicated) were given in g/100 mL. IR spectra (ν cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H NMR spectra were obtained ($CDCl_3$ unless otherwise indicated, Me_4Si, δ = 0 ppm) from Bruker AC250, AM300 ; coupling constants J values are given in Hertz (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet respectively). ^{13}C NMR spectra were recorded on AC200 (50.0 MHz)



Scheme 3

or AM300 (75.0MHz). Mass spectra and high resolution mass spectra were respectively measured on an AEI MS50 and on a Kratos MS80 spectrometer. Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that the organic layer was dried over magnesium sulfate, filtered, and evaporated under *vacuum*.

(2*R*, 5*R*, 6*S*)-6-hydroxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane-8-one 6

A solution of epoxide **5** (868 mg, 4.0 mmol) in anhydrous THF (8.0 mL) and MeOH (4.0 mL) was added dropwise under argon to a stirred solution of SmI_2 (0.1 M in THF, 80.0 mL, 8.0 mmol) at -78°C. After being stirred 0.5 h at -78°C, a saturated aqueous solution of K_2CO_3 (50 mL) was added, the mixture was allowed to reach room temperature and was extracted with Et_2O. The crude

product obtained after usual workup was purified by flash chromatography (eluent CH_2Cl_2-MeOH 95:5) and afforded the alcohol **6** as white crystals (833 mg, 95%). mp : 132-134°C. $[\alpha]_D^{30} = +231$ (c = 0.87). lit. : mp 128°C, $[\alpha]_D^{20} = +228$ (c = 0.20). Comparison of ^1H and ^{13}C NMR data.[19]

(2*R*, 5*R*, 6*S*)-6-benzoyloxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane-8-one 7

To a stirred solution of alcohol **6** (776 mg, 3.54 mmol) in dry CH_2Cl_2 (15.0 mL) at 0°C were successively added Et_3N (0.56 mL, 4.03 mmol) and benzoyl chloride (0.468 mL, 4.03 mmol). The mixture was stirred at room temperature until completion of the reaction. Then a saturated aqueous solution of NH_4Cl (9.0 mL) and CH_2Cl_2 (20 mL) were added. The aqueous layer was again extracted with CH_2Cl_2 (2 x 20 mL) and the organic layers were washed with a solution of Na_2CO_3 (10% w/v, 2 x 7 mL) and a saturated aqueous solution of NH_4Cl. The crude product obtained after usual workup was purified by chromatography (eluent : heptane-EtOAc 1:1) to get benzoate **7** as a colorless oil (1.143 g, 100%). $[\alpha]_D^{20} = +138$ (c = 0.73). IR : 1730, 1605. ^1H NMR (250 MHz) : 8.01 (2H, Ar-H), 7.6-7.3 (8H, Ar-H), 6.41 (s, 1H, H-2), 5.32 (m, 1H, H-6), 4.46 (dd, 1H, J = 8.7, J' = 6.8, Ha-4), 4.14 (m, 1H, H-5), 3.92 (dd, 1H, J = J' = 8.3, Hb-4), 3.14 (m, 2H, H_2-7). ^{13}C (75.0 MHz) = 174.40 (CO), 166.46 (CO), 138.27 (qC, Ar), 133.87, 129.83, 128.96, 128.84, 128.72, 128.60, 126.08 (CH, Ar), 87.47 (C-2), 72.47 (C-6), 70.46 (C-4), 65.46 (C-5), 40.11 (C-7). MS : 323 ($M^{+\cdot}$), 246, 201, 105, 95, 77. Anal. calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33; found : C, 70.72; H, 5.34; N, 4.42.

(4*S*, 5*R*)-4-benzoyloxy-5-hydroxymethylpyrrolidin-2-one 8

A solution of trifluoroacetic acid (1.0 mL) in a mixture THF-H_2O 1:1 (4 mL) was added under argon to a stirred solution of compound **7** (872 mg, 2.7

mmol) in THF-H_2O 1:1 (4 mL). After being stirred at room temperature for 6 h, the solvents were removed under reduced pressure and by evaporation of toluene. The residue was purified by chromatography (eluent : CH_2Cl_2-MeOH 9:1) to afford the alcohol **8** as a white solid (577 mg, 91%). mp 135-137°C. $[\alpha]_D^{32} = -15$ (c : 1.68, MeOH). IR : 3643, 3443, 3006, 2950, 2843, 1706, 1631, 1612, 1450. ^1H NMR (300 MHz) : 8.05 (d, 2H, Ar-H), 7.64 (dd, 1H, Ar-H), 7.47 (dd, 2H, Ar-H), 6.17 (s, 1H, attributed to NH), 5.44 (br d, 1H, H-4), 3.86 (m, 3H, H_2-6, H-5), 2.96 (dd, 1H, J = 18, J' = 7, Ha-3), 2.58 (dd, 1H, J = 18, J' ~ 1.5, Hb-3). ^{13}C NMR (75.0 MHz, CD_3OD : 49.0 ppm) : 178.10 (CO), 167.44 (CO), 134.55, 130.67, 129.65 (CH, Ar), 74.03 (C-4), 64.25 (C-5), 63.48 (OCH_2), 38.43 (C-3). (FAB) MS : 236 $(M + H)^+$, 154, 136, 114, 109, 105. HRMS for $C_{12}H_{14}NO_4$ [$(M + H)^+$] calcd 236.0922; found 236.0962. Anal. calcd for $C_{12}H_{13}NO_4.H_2O$: C, 56.91; H, 5.97; N, 5.53; found : C, 57.19; H, 5.82; N, 5.64.

(4*S*, 5*R*)-4-benzoyloxy-5-(1-ethoxyethoxymethyl)pyrrolidin-2-one 9

Ethyl vinyl ether (0.50 mL, 5.2 mmol) and trichloroacetic acid (29 mg, 0.18 mmol) were successively added under argon to a solution of alcohol **8** (409 mg, 1.74 mmol) in $CHCl_3$ (20 mL) at 0°C. The flow of argon was removed and the mixture was stirred at room temperature for 6 h. A saturated aqueous solution of $NaHCO_3$ (8 mL) was added at the completion of the reaction. After being stirred for 15 min., the mixture was extracted with CH_2Cl_2 and the organic layers were washed with a saturated aqueous solution of $NaHCO_3$. After usual workup the crude product was purified by chromatography (eluent : CH_2Cl_2-MeOH 95:5) to give compound **9** (476 mg, 89%) as a colorless oil. IR : 3481, 2982, 1706, 1603. ^1H NMR (300 MHz) : 8.01 (m, 2H, Ar-H), 7.58 (dd, 1H, Ar-H), 7.43 (dd, 2H, Ar-H), 6.90 (d, 1H, NH), 5.39 (m, 1H, H-4), 4.72 (m, 1H, OCHO), 3.91 (m, 1H, H-5), 3.75, 3.63, 3.48 (4H, 2 x OCH_2), 2.93 (dd, 1H, $J_{3a,3b}$ = 17, Ha-3), 2.51

(dd, 1H, J = 17, Hb-3), 1.31 (d, 3H, $CHC\underline{H}_3$), 1.20 (2t, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75.0 MHz) : 175.64 (CO), 166.15 (CO), 133.54; 129.77, 128.57 (CH, Ar), 99.93 (OCHO), 72.44-72.26 (C-4), 65.69-65.55 (OCH_2), 61.35 (OCH_2), 60.90-60.79 (C-5), 37.21 (C-3), 19.66 ($CH\text{-}\underline{C}H_3$), 15.32 ($CH_2\text{-}\underline{C}H_3$). MS : 278 $(M\text{-}Et)^{+\bullet}$, 262, 218, 204, 155, 73.

(4*S*, 5*R*)-4-benzoyloxy-1-*tert*-butoxycarbonyl-5-(1-ethoxyethoxymethyl)-pyrrolidin-2-one 10

DMAP (15 mg, 0.12 mmol) was added under argon to a stirred solution of pyrrolidinone **9** (406 mg, 1.32 mmol) in dry CH_2Cl_2 (6.0 mL). A solution of $(Boc)_2O$ (576 mg, 2.64 mmol) in dry CH_2Cl_2 (2.4 mL) was added and the mixture was stirred at room temperature for 12 h. A saturated aqueous solution of citric acid (3 mL) was added and the mixture was extracted with CH_2Cl_2 to give crude product after usual workup (655 mg). This product was **rapidly** filtered on silica gel (eluent : Et_2O) to afford **10** as a colorless oil (537 mg, 100%). IR : 3000, 1785, 1750, 1722, 1476, 1462. ^1H NMR (250 MHz) : 8.02 (d, 2H, Ar-H), 7.60 (dd, 1H, Ar-H), 7.47 (dd, 2H, Ar-H), 5.42 (d, 1H, $J_{3a,4} = 6.7$, H-4), 4.74 (m, 1H, OCHO), 4.34 (m, 1H, H-5), 4.1-3.8 (m, 2H, OCH_2), 3.60 and 3.44 (2m, 2H, $OC\underline{H}_2CH_3$), 3.19 (ddd, 1H, J = 18.2, J' = 6.7; J'' = 3, Ha-3), 2.65 (br d, 1H, J = 18.2, Hb-3), 1.57 (2s, 9H, *t*-Bu), 1.30 (2d, 3H, $CHC\underline{H}_3$), 1.20 (t, 3H, CH_2CH_3). ^{13}C NMR (75.0 MHz) : 172.19 (CO), 166.16 (CO), 149.56 (NCO_2), 133.6, 129.83, 128.60 (CH, Ar), 99.79-99.51 (OCHO), 83.56 (qC, *t*-Bu), 70.48 (C-4), 64.41 (C-5), 63.18-62.88 (OCH_2), 61.77-60.91 (OCH_2), 39.46 (C-3), 28.1 (CH_3, *t*-Bu), 19.60 ($CH\underline{C}H_3$), 15.29 ($CH_2\underline{C}H_3$). Anal. calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N, 3.44; found : C, 61.66; H, 7.21; N, 3.34.

(2*R*, 3*S*)-3-benzoyloxy-1-*tert*-butoxycarbonyl-2-(1-ethoxyethoxymethyl)-5-hydroxypyrrolidines 11

A solution of DIBAL-H in hexanes (1M, 1.83 mL, 1.83 mmol) was added dropwise under argon to a stirred solution of pyrrolidinone **10** (495 mg, 1.22 mmol) in THF (3.0 mL) at -78°C. After being stirred at -78°C for additional 20 min., a saturated aqueous NH_4Cl solution (4.5 mL), CH_2Cl_2 (50 mL) and an aqueous Na_2CO_3 solution (5% w/v, 6 mL) were successively added. The mixture was stirred at room temperature for 15 min. and extracted with CH_2Cl_2 to give **11** after usual workup (473 mg, 95%). IR : 3525, 3010, 1720, 1680 (sh). ^1H NMR (300 MHz) : 8.02 (2H, Ar-H), 7.58 (1H, Ar-H), 7.46 (2H, Ar-H), 5.8-5.4 (H-5, H-3), 4.80 (OCHO), 4.3-3.4 (2xOCH_2, H-2), 2.4, 2.2 (H_2-4), 1.59-1.50 (*t*-Bu), 1.36 (2d, 3H, $CHCH_3$), 1.21 (2t, 3H, CH_2CH_3).

(2*R*, 3*S*)-3-benzoyloxy-1-*tert*-butoxycarbonyl-2-hydroxymethyl-5-methoxypyrrolidines 12

A solution of *p*-toluenesulfonic acid in methanol (0.10 g/100 mL, 9.3 mL) was added under argon to α-hydroxycarbamates **11** (422 mg, 1.03 mmol) at room temperature. The mixture was stirred for 1.25 h before addition of Na_2CO_3 (10% w/v) and extraction with CH_2Cl_2. Usual workup afforded α-methoxycarbamates **12** as a mixture of diastereomers (362 mg, 100%). The diastereomers could be separated by preparative TLC for spectral analysis (eluent : CH_2Cl_2-MeOH 97:3). ***Major diastereomer 12a (less polar)*** : $[\alpha]_D^{27}$ = - 19 (c = 1.20). IR : 3550, 3030, 1710, 1630. ^1H NMR (300 MHz) : 8.01 (d, 2H, Ar-H), 7.57 (dd, 1H, Ar-H), 7.44 (dd, 2H, Ar-H), 5.6-5.3 (2H, H-3, H-5), 4.24-4.11 (H-2), 3.84 (m, 2H, OCH_2), 3.40 (br s, 3H, OCH_3), 2.52 (m, 1H, Ha-4), 2.25 (m, 1H, Hb-4), 1.51 (s, 9H, *t*-Bu). ^{13}C NMR (50.0 MHz) : 133.4, 129.7, 128.5 (CH, Ar), 88.6 (C-5), 81.4 (qC,

t-Bu), 75.2 (C-3), 66.0-65.3 (C-2), 64.6-63.2 (OCH_2), 55.7 (OCH_3), 38.9 (C-4), 28.3 (CH_3, *t*-Bu). MS : 320 $(M\text{-}OCH_3)^{+\cdot}$, 264, 220, 188, 105 (100%), 98, 57. Anal. calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99; found : C, 61.56; H, 7.32; N, 3.92. ***Minor diastereomer 12b*** : $[\alpha]_D^{30} = -6$ (c = 1.87). IR : 3625, 3500, 3010, 1715, 1610, 1400, 1365. ^1H NMR (300 MHz) : 8.06 (d, 2H, Ar-H), 7.57 (dd, 1H, Ar-H), 7.45 (dd, 2H, Ar-H), 5.4-5.0 (2H, H-3, H-5), 4.19-4.05 (H-2), 3.93-3.84 (OCH_2), 3.39 (br s, OCH_3), 2.32 (ddd, 1H, Ha-4), 2.19 (br d, 1H, Hb-4), 1.50 (s, 9H, *t*-Bu). ^{13}C NMR (50.0 MHz) : 133.3, 129.9, 128.5 (CH, Ar), 90.1 (C-5), 81.2 (qC, *t*-Bu), 76.0 (C-3), 66.2 (C-2), 63.4-62.4 (OCH_2), 56.5 (OCH_3), 36.7 (C-4), 28.5 (CH_3, *t*-Bu). MS : 320 $(M\text{-}OCH_3)^{+\cdot}$, 264, 229, 220, 188 (100%), 173, 156, 129, 105, 98, 77, 57. (IC) HRMS : calcd for $C_{18}H_{26}NO_6$ $(M + H)^+$: 352.1760; found : 352.1787.

(2*S*, 5*R*)-4-benzoyloxy-1-tert-butoxycarbonyl-2-cyano-5-hydroxymethylpyrrolidine 13

A solution of $SnCl_4$ in dry CH_2Cl_2 (0.43 M, 0.25 mL, 0.107 mmol) and then Me_3SiCN (96 µL, 0.72 mmol) were successively added under argon to crude α-methoxycarbamates **12** (126 mg, 0.36 mmol) at -40°C. After being stirred at -40°C for 45 min., an aqueous solution of Na_2CO_3 (10% w/v) was added, the cooling bath was removed and the mixture was extracted with CH_2Cl_2. The products were separated by preparative TLC (eluent : CH_2Cl_2-MeOH 97:3) to afford unreacted **12a** (23 mg) and two main products. The less polar silylated derivative was unstable and gave quantitatively the more polar compound **13** which was isolated in 50% yield (62.1 mg, 61% from converted **12**). mp : 125-127°C. $[\alpha]_D^{26} = -63$ (c = 0.30). IR : 3640, 3458, 2987, 2225 (very weak), 1714 (broad), 1602. ^1H NMR (300 MHz) : 8.14 (d, 2H, Ar-H), 7.58 (dd, 1H, Ar-H), 7.47 (dd, 2H, Ar-H), 5.51 (1H, H-4), 4.65 (d, 1H, $J_{2,3a} = 7$, H-2), 4.20 (m, 1H, H-

5), 3.94, 3.82 (2H, OCH_2), 2.72 (m, 1H, Ha-3), 2.45 (d, 1H, J ≃ 15, Hb-3). ^{13}C NMR (75.0 MHz) : 133.68, 130.17, 128.71 (CH, Ar), 118.82 (CN), 81.2 (qC, *t*-Bu), 75.94 (C-4), 66.14 (C-5), 62.41 (OCH_2), 47.42 (C-2), 35.96 (C-3), 28.45 (CH_3, *t*-Bu). (IC) MS : 347 $(M + H)^+$, 320 (100%), 291, 220, 198, 180. (IC) HRMS calcd for $C_{18}H_{23}N_2O_5$ [$(M + H)^+$] : 347.1606; found: 347.1575.

(-) Bulgecinine 1

A solution of nitrile **13** (50 mg, 0.14 mmol) in 6N HCl (5.0 mL) was heated under reflux for 24 h to afford the aminoacid hydrochloride after evaporation to dryness. This product in EtOH (1.2 mL) was treated with propylene oxide (0.2 mL). After being stirred for 16 h and evaporated to dryness, the residue was disolved in H_2O, filtered and the solution was evaporated to dryness to give (-) bulgecinine **1** (23.3 mg, 100%). $[\alpha]_D^{27} = -16$ (c = 0.20, H_2O) ; lit. : $[\alpha]_D^{27} = -15.6$ (c = 0.53, H_2O).[4b] Comparison of ^1H NMR data (D_2O).[1a]

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