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An efficient, stereoselective synthesis of (−)-bulgecinine from (*S*)-aspartic acid †

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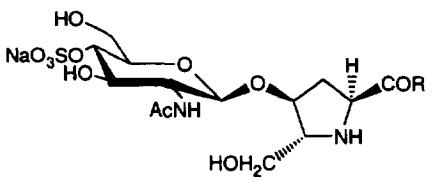
Abstract: A stereoselective synthesis of (2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethylproline **1** starting from (*S*)-aspartic acid **2** is described. The key step of the synthesis is the $[Rh(OAc)_2]_2$ catalyzed stereospecific transformation (de >98%) of the hexafluoroacetone protected diazoketone **5** into the 4-oxoproline derivative **7**. The keto function of **7** was reduced with high diastereoselectivity (de >88%) to give the 4-cis-hydroxyproline derivative **8**. After deprotection (−)-bulgecinine **1** was obtained from **9** on reduction of the ester moiety with $LiBHEt_3$. © 1997 Elsevier Science Ltd

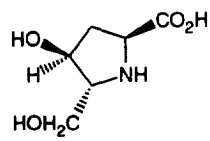
Introduction

A new class of glycopeptides of low molecular weight named bulgecin A, B, and C was isolated from culture broths of *Pseudomonas acidophila* and *Pseudomonas mesoacidophila* by Shinagawa and coworkers.[1] These microorganisms also produce β-lactam antibiotics like sulfacezin and isosulfacezin. In cooperation with these antibiotics bulgecins induce characteristic morphological changes in the cell wall of Gram-negative bacteria resulting in an enhanced sensitivity of the organism to β-lactams. Bulgecins themselves show no antibacterial activity at all.[1a]

Because of this remarkable synergistic effect, the bulgecin aglycon bulgecinine [(2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethylproline] **1** is of current interest. Syntheses from various educts have been described.[2] We now report on a synthesis of bulgecinine starting from (*S*)-aspartic acid using hexafluoroacetone as a stereocontrolling protective group.[3]



Bulgecin A: R= $NHCH_2CH_2SO_3H$
Bulgecin B: R= $NHCH_2CH_2CO_2H$
Bulgecin C: R= OH



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Results and discussion

Hexafluoroacetone reacts with α-amino acids to give five membered lactones protecting simultaneously the amino and adjacent carboxylic group. In the case of aspartic acid **2** the [(4*S*)-2,2-bis(trifluoromethyl)-5-oxo-1,3-oxazolidine-4-yl]acetate **3** is exclusively formed on reaction with hexafluoroacetone in dimethyl sulfoxide.[3,4] The ω-carboxylic group remains unaffected. Therefore, via this route regiospecific derivatizations of the ω-carboxylic group can be achieved. On the other hand, the lactone represents an α-carboxy-activated species which can be derivatized regioselectively at the α-carboxylic group on reaction with nucleophiles.[5]

† Dedicated to Professor Dr Peter Welzel on the occasion of his 60th birthday

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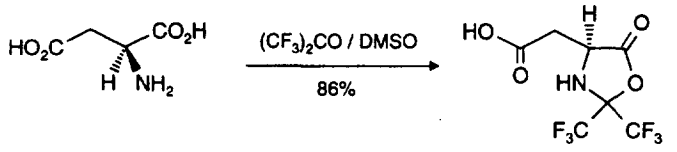


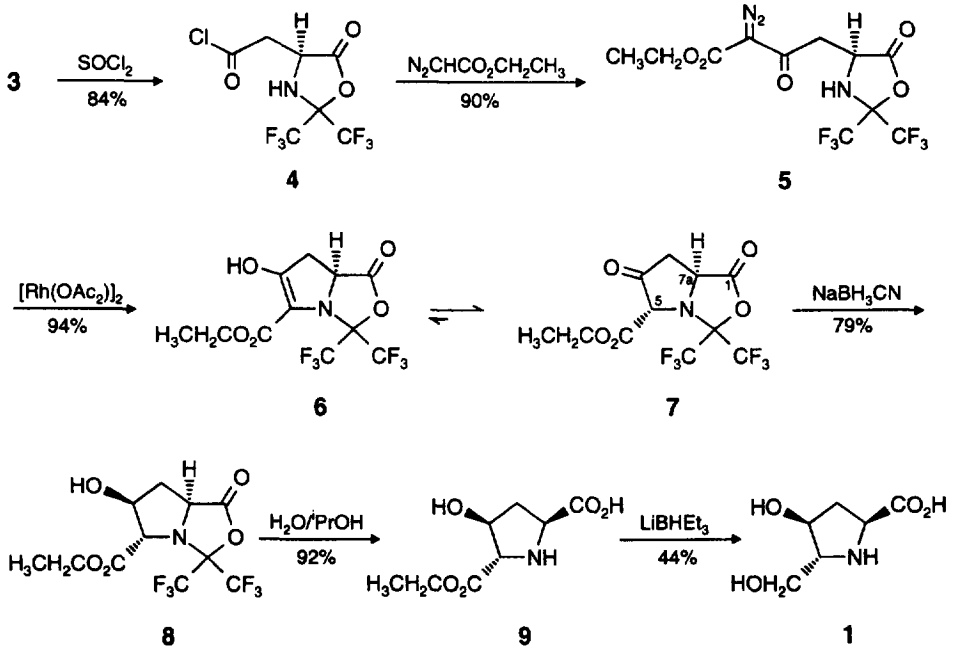
2 3

On treatment of **3** with thionyl chloride the acid chloride **4** is formed which reacts with ethyl diazo acetate to give **5** containing a diazo function in the side chain.[6] Transition metal catalyzed reactions of α-diazocarbonyl compounds proceed via electrophilic Fischer-type carbene complexes[7] suppressing the Wolff rearrangement completely. Consequently, when α-diazoketone **5** is treated at room temperature with catalytic amounts of $[Rh(OAc)_2]_2$ for a controlled decomposition the ^{19}F NMR spectrum shows the formation of a single NH insertion product, which we assign an enol structure **6** based on the NMR data. The crystalline compound **6** can be stored at −28°C over longer periods. At room temperature in both the solid state and in solution **6** tautomerizes to give the expected 4-oxoproline derivative **7**.[8]

As a result of the concave shape of the bicyclic system **7** whose inner face is sterically shielded by one of the trifluoromethyl groups nucleophilic addition reactions to the carbonyl group should display a distinct preference for the *Re* face. This was confirmed by reduction of the keto function of **7** with $NaBH_3CN$ (de >88%). The diastereoisomers were separated by flash-chromatography.

On treatment with 2-propanol/water at room temperature the lactone can be cleaved under neutral conditions to yield the unprotected amino acid **9** in nearly quantitative yield. Finally, the regioselective reduction of the ester group of **9** to provide bulgecinine **1** can be achieved on treatment with $LiBHEt_3$ in tetrahydrofuran.

The relative configuration of the newly formed chiral centres at C-4 and C-5 of compound **1** with respect to C-2 was proven by a series of NOE difference experiments.



Experimental[9]

(7aS)-6-Hydroxy-1-oxo-3,3-bis(trifluoromethyl)-7,7a-dihydro-pyrrolo[1,2-c]oxazole-5-carboxylic acid ethyl ester 6

To a stirred solution of **5** (3.20 g, 8.5 mmol) in trichloromethane (80 mL) at room temperature under N_2 $[Rh(OAc)_2]_2$ (12 mg, 27 μmol) was added. After 2 h the reaction was complete (^{19}F NMR analysis). The solvent was removed in vacuo and the residue extracted with hexane (3×100 mL). The combined hexane extracts were concentrated in vacuo to dryness giving **6** as a crystalline substance which had already undergone partially a conversion into **7** (ca. 10%), but which did not react further when stored at −28°C. ^1H NMR (360.3 MHz, $CDCl_3$, TMS) δ 1.31 (t, $^3J(H,H)$=7.2 Hz, 3H; CH_3); 2.94 (dd, $^2J(H,H)$=17.9 Hz, $^3J(H,H)$=11.1 Hz, 1H; C(7)-H); 3.24 (dd, $^2J(H,H)$ =17.9 Hz, $^3J(H,H)$=10.2 Hz, 1H; C(7)-H); 4.31–4.39 (m, 2H; OCH_2); 4.75 (dd, $^3J(H,H)$=10.2 Hz, $^3J(H,H)$=11.1 Hz, 1H; C(7a)-H); 10.19 (s, br., 1H; OH); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.6 (CH_3); 33.9 (C-7); 59.1 (C-7a); 61.5 (OCH_2); 92.5 (m, C-3); 109.5 (C-5); 119.9 (q, $^1J(C,F)$=291 Hz; CF_3); 120.2 (q, $^1J(C,F)$=286 Hz; CF_3); 165.7 (C-6); 166.6, 168.7 (C=O ester, C-1); ^{19}F NMR (235.3 MHz, $CDCl_3$)[10] δ −1.1 (q, $^4J(F,F)$=8.1 Hz, 3F; CF_3); 3.7 (q, $^4J(F,F)$=8.1 Hz, 3F; CF_3).

(5S,7aS)-1,6-Dioxo-3,3-bis(trifluoromethyl)-tetrahydro-pyrrolo[1,2-c]oxazole-5-carboxylic acid ethyl ester 7

Compound **6** was dissolved in trichloromethane (10 mL). The solution was filtered through a pad of silica gel (90×70 mm, 0.032–0.063 mm). The silica gel column was washed with trichloromethane (5×50 mL) and the filtrate was concentrated to dryness in vacuo. **7** was obtained as colorless oil (**5** → **7**: 2.77 g, 94%, de >98%[11]). $[\alpha]_D^{21}$ −104.5 (c 2.0, $CHCl_3$); ^1H NMR (360.3 MHz, $CDCl_3$, TMS) δ 1.31 (t, $^3J(H,H)$=7.1 Hz, 3H; CH_3); 2.71 (dd, $^2J(H,H)$=18.9 Hz, $^3J(H,H)$=9.0 Hz, 1H; C(7)-H); 2.94 (dd, $^2J(H,H)$=18.9 Hz, $^3J(H,H)$=8.5 Hz, 1H; C(7)-H); 4.23–4.32 (m, 2H; OCH_2); 4.46 (s, 1H; C(5)-H); 4.77 (dd, $^3J(H,H)$=8.5 Hz, 9.0 Hz; 1H, C(7a)-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.9 (CH_3); 37.1 (C-7); 56.3 (C-7a); 62.9 (OCH_2); 66.1 (C-5); 91.3 (qq, $^2J(C,F)$=32 Hz; C-3); 120.0 (q, $^1J(C,F)$=291 Hz; CF_3); 121.1 (q, $^1J(C,F)$=287 Hz; CF_3); 165.2, 167.9 (C=O ester, C-1); 201.9 (C-6); ^{19}F NMR (235.3 MHz, $CDCl_3$) δ −3.1 (q, $^4J(F,F)$=9.0 Hz, 3F; CF_3); 4.9 (q, $^4J(F,F)$=9.0 Hz, 3F; CF_3); IR (film) ν 1830, 1770, 1740 cm^{-1}; GCMS(EI) *m/z* 349 (M^+); 303; 276; 110; 54; Anal. Calcd for $C_{11}H_9F_6NO_3$: C, 37.84; H, 2.60; N, 4.01. Found C, 37.83; H, 2.60; N, 4.21.

(5S,6S,7aS)-6-Hydroxy-1-oxo-3,3-bis(trifluoromethyl)-tetrahydro-pyrrolo[1,2-c]oxazole-5-carboxylic acid ethyl ester 8

To a stirred solution of **7** (1.82 g, 5.2 mmol) in absolute 2-propanol (5–10 mL) $NaBH_3CN$ (0.16 g, 2.6 mmol) was added at 0°C. The reaction mixture was adjusted to pH 3–4 with acetic acid. After 1 h, monitoring by ^{19}F NMR-spectroscopy showed the complete consumption of the educt. The reaction mixture was taken up in trichloromethane (200 mL), washed with aqueous $NaHCO_3$ (sat.) and water. The organic layer was separated and dried ($MgSO_4$). After removal of the solvent in vacuo the cis-product **8** was separated from the diastereomeric mixture (de >88%) by flash-chromatography (eluent CH_2Cl_2/ethyl acetate 10:1) and isolated as a white solid (1.43 g, 79%). mp 80–82°C; $[\alpha]_D^{20}$=−37.0 (c 1.0, $CHCl_3$); ^1H NMR (360.3 MHz, $CDCl_3$, TMS) δ 1.28 (t, $^3J(H,H)$=7.2 Hz, 3H; CH_3); 2.29 (dm, $J_{AB}(H,H)$=13.4 Hz, 1H; C(7)-H); 2.47 (dm, $J_{AB}(H,H)$=13.4 Hz, 1H; C(7)-H); 3.21 (s, br., 1H; OH); 4.21 (q, $^3J(H,H)$=7.2 Hz, 2H; OCH_2); 4.26–4.29 (m, 2H; C(5)-H, C(7a)-H); 4.59 (m, 1H; C(6)-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.7 (CH_3); 35.7 (C-7); 60.9 (q, br., $^4J(C,F)$=2.0 Hz; C-7a); 61.9 (OCH_2); 69.8 (q, br., $^4J(C,F)$=2.0 Hz; C-5); 73.4 (C-6); 91.9 (qq, $^2J(C,F)$=32 Hz, $^2J(C,F)$=32 Hz; C-3); 119.5 (q, $^1J(C,F)$=289 Hz; CF_3); 121.2 (q, $^1J(C,F)$=289 Hz; CF_3); 169.8 (C=O lactone); 171.7 (C=O ester); ^{19}F NMR (235.3 MHz, $CDCl_3$) δ −1.7 (q, $^4J(F,F)$=10.5 Hz, 3F; CF_3); 7.1 (q, $^4J(F,F)$=10.5 Hz; 3F); IR (KBr) ν 3490, 1845, 1760 cm^{-1}; GCMS(EI) m/z 351 (M^+); 305; 278; 112; Anal. Calcd for $C_{11}H_{11}F_6NO_5$: C, 37.62; H, 3.16; N, 3.99. Found C, 37.91; H, 3.39; N, 4.29.

(2S,3S,5S)-3-Hydroxypyrrolidine-2,5-dicarboxylic acid 2-ethyl ester **9**

8 (1.65 g, 4.7 mmol) was dissolved in 2-propanol (20 mL) and water (20 mL) was added. The reaction mixture was stirred at room temperature until the reaction was complete (monitored by ^{19}F NMR, 18–24 h). After removal of the solvent the crude product was taken up in ether and stirred for 0.5 d, filtered and **9** was obtained as a white solid (0.88 g, 92%). mp 184°C; $[\alpha]_D^{21}$=+25.5 (c 1.0, H_2O); ^1H NMR (250.1 MHz, D_4-methanol) δ 1.32 (t, ^3J(H,H)=7.1 Hz, 3H; CH_3); 2.23 (dm, J_{AB}(H,H)=14.0 Hz, 1H; C(4)-H); 2.43 (dm, J_{AB}(H,H)=14.0 Hz, 1H; C(4)-H); 4.16 (m, 1H; C(5)-H); 4.30 (q, ^3J(H,H)=7.1 Hz, 2H; OCH_2); 4.32 (d, ^3J(H,H)=3.3 Hz, 1H; C(2)-H); 4.54 (m, 1H; C(3)-H); ^{13}C NMR (50.3 MHz, D_4-methanol): δ 14.3 (CH_3); 37.6 (C-4); 61.1 (C-5); 64.1 (OCH_2); 68.5 (C-2); 74.3 (C-3); 168.8 (C=O lactone); 173.6 (C=O ester); IR (KBr) ν 3230, 3160, 2975, 1730, 1720, 1635, 1575 cm^{-1}; MS(EI) m/z 203 (M^+), 158, 130; Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found C, 47.42; H, 6.54; N, 6.87.

(2S,4S,5R)-4-Hydroxy-5-hydroxymethylproline (bulgecinine) 1

Excess $LiBHEt_3$ (1M in THF, 9.0 mmol, 9.0 mL) was added dropwise to **9** (0.24 g, 1.2 mmol) in absolute THF (2.3 mL) under argon atmosphere at 0°C. The reaction mixture was stirred at room temperature for 1 h followed by acidification to pH 6 with 1 N HCl and was then evaporated to dryness. The crude product was dissolved several times in ethanol and methanol and evaporated to dryness to remove the excess of $LiBHEt_3$. Purification by flash-chromatography (eluent methanol/water 20:1), ion exchange chromatography (1 M aqueous pyridine) followed by recrystallization from ethanol/water afforded bulgecinine **1** as white needles (0.09 g, 44%). mp 180–188°C (ethanol/water, decom.) (lit. mp 182°C)[1a]; $[\alpha]_D^{21}$=−12.1 (c 1.4, H_2O) (lit. $[\alpha]_D^{20}$=−13.1, c 0.95, H_2O)[1b]; CD[12] (c=1mg/mL, H_2O): $\Delta\epsilon_{210.6}$=+0.356[1b]; ^1H NMR (360.3 MHz, D_2O) δ 2.08 (ddd, ^2J(H,H)=13.8 Hz, ^3J(H,H)=6.5 Hz, ^3J(H,H)=5.1 Hz, 1H; C(3)-H); 2.59 (ddd, ^2J(H,H)=13.8 Hz, ^3J(H,H)=9.0 Hz, ^3J(H,H)=5.9 Hz, 1H; C(3)-H); 3.63–3.71 (m, 2H; C(5)-H, OCH_2); 3.81 (m, 1H; OCH_2); 4.11 (dd, ^3J(H,H)=9.0 Hz, ^3J(H,H)=6.5 Hz, 1H; C(2)-H); 4.31 (m, 1H; C(4)-H); ^{13}C NMR (90.6 MHz, D_2O) δ 37.3 (C-3); 59.1 (OCH_2); 59.9 (C-2); 67.4 (C-5); 71.4 (C-4); 175.4 (C=O); IR (KBr) ν 3400–2940, 1628, 1405, 1084, 1044 cm^{-1}; HRMS (FAB) Calcd for [M+H$^+$], $C_6H_{12}NO_4$: 162.076633, Found m/z 162.077000.

Acknowledgements

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9. Melting points (uncorrected): Tottoli apparatus (Büchi SMP-20) or Boetius hot stage microscope. IR spectra: Perkin-Elmer spectrometers 157 G and 257. NMR: Bruker AM 360/AC 250/AC 200. Elemental analyses: C,H,N analyser EA 415/0, Monar System (Heraeus). Optical rotations: Perkin-Elmer 241 MC polarimeter (Na-D-line). CD spectrometer: Jasco J-715. GC/MS: HP 5890 with coupling to HP 5972 A MSD (Hewlett-Packard) 30 m column HP 5-MS. Mass spectra (EI): Varian MAT CH5 (70 eV). High resolution MS: Fisons VG Autospec. Chromatography: ion-exchange resin (hydrogen form): Amberlite IR-120, 16–45 mesh; flash silica gel (Riedel-de-Haën) 30–63 μm; reversed-phase silica gel (Merck, 60 silanized) 63–200 μm.
10. Trifluoroacetic acid as external standard.
11. Determined by ^{19}F NMR.
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