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SYNTHESIS OF BULGECININE: A NEW AMINO ACID IN BULGECINS[1)]

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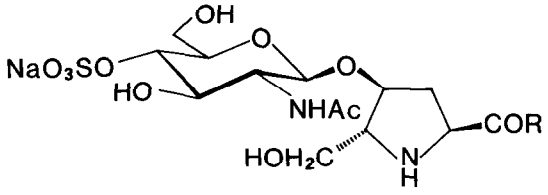
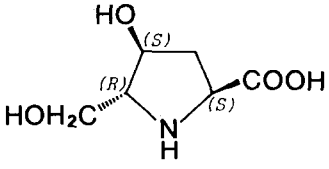
Summary: Bulgecinine, a new proline type amino acid in bulgecins, was synthesized stereospecifically by use of D-glucose as a chiral precursor.

A new amino acid of proline analog had been found as a common constituent of bulgecins (**1**) which are unique glycopeptides produced by *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*.[2)] Bulgecins induce a characteristic morphological change called bulge formation in Gram-negative bacteria in cooperation with β-lactam antibiotics such as sulfazecin or isosulfazecin which was also produced by *P. acidophila* and *P. mesoacidophila*, respectively. As a result of bulge formation, the activity of these antibiotics is effectively enhanced. The structure of the new amino acid in bulgecins had been determined chemically and crystallographically to be (2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethylproline by Shinagawa *et al.*[3)] This amino acid is now named bulgecinine (**2**).

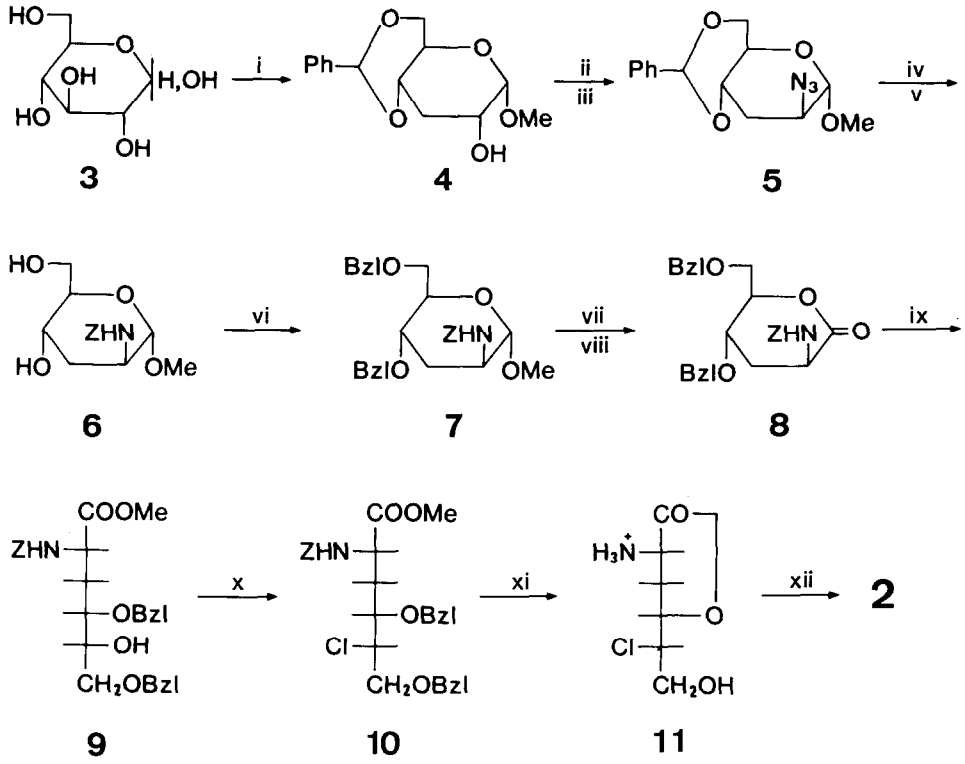


1 Bulgecin A: R = $NHCH_2CH_2SO_3H$
B: R = $NHCH_2CH_2COOH$



2 Bulgecinine

Synthesis of bulgecinine was carried out by use of D-glucose (**3**) as a chiral precursor. The synthetic route is shown in Scheme 1. 3-Deoxy-D-glucose derivative (**4**) possessing a suitable carbon framework was first prepared by $LiAlH_4$ reduction of 2,3-ditosyl derivative of D-glucose according to the procedure reported by Vis *et al.*[4)] Hydroxyl group at C-2 of the compound **4** was then substituted with azide group *via* tosylate accompanying an inversion of the configuration.[5)] Amino sugar obtained by hydrogenolysis of the compound **5** was isolated as *N*-benzyloxycarbonyl derivative **6**. After the protection of hydroxyl groups, methyl glycoside was hydrolyzed and then oxidized to



Scheme 1. i) Ref. 4; ii) TsCl, pyridine, 88%; iii) NaN_3, DMF, 73%; iv) H_2, Pd black, MeOH(containing 1eq HCl), quantitative; v) *N*-benzyloxycarbonyloxysuccinimide (ZOSu), $(C_2H_5)_3N$, MeOH, 92%; vi) BzlBr, NaOH, DMF, 61%; vii) *c*.HCl, AcOH, 66%; viii) PDC, CH_2Cl_2, 59%; ix) MeOH, reflux, quantitative; x) PPh_3, CCl_4 (Ref. 6), 43%; xi) H_2, Pd black, MeOH, *c*.HCl, quantitative; xii) sat. $Ba(OH)_2$, pH 9.0, 75%.

prepare δ-lactone compound **8**. δ-Hydroxyl group freed by methanolysis of **8** was chlorinated with PPh_3 and CCl_4[6] accompanying an inversion of the configuration on δ-carbon atom. Final cyclization was carried out after the removal of all protecting groups. γ-Lactone compound **11** obtained by hydrogenolysis of the chloro derivative **10** under acidic condition was successfully converted into bulgecinine (**2**) by treatment with saturated $Ba(OH)_2$ solution. Synthetic bulgecinine was completely identical with the natural compound in all respects.[7]

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References

1) A part of this work was presented at the 50th National Meeting of the Chemical Society of Japan, Tokyo, April 1985, Abst. No. 1N31.
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7) For example: $[\alpha]_D^{29}$-13°(*c* 0.75, H_2O) [lit. $[\alpha]_D^{20}$-13.1°(*c* 0.95, H_2O)[3)]].

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