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SYNTHESIS OF DEHYDROXYMETHYLBULGECIN A[1)]

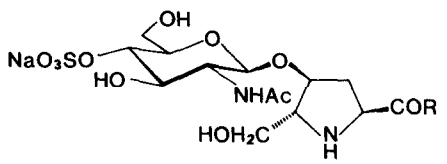
Tateaki Wakamiya, Keiko Yamanoi, Kayoko Kanou, and Tetsuo Shiba*
Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan

Summary: The dehydroxymethyl analog of bulgecin A was synthesized in order to establish a synthetic route of bulgecin A.

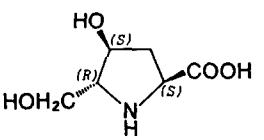
O-Sulfated glycopeptides, bulgecin A (**1**) and B (**2**), were isolated from the culture broth of Pseudomonas acidophila and Pseudomonas mesoacidophila.[2)] These compounds introduced a characteristic morphological change called bulge formation in Gram-negative bacteria in cooperation with β-lactam antibiotics such as sulfazecin or isosulfazecin which was also produced by P. acidophila or P. mesoacidophila, respectively. As a result of the bulge formation, the activity of these antibiotics was effectively enhanced. However, the sole use of bulgecins did not cause the morphological change at all. Recently two similar potentiators of β-lactam antibiotics, SQ 28504 and SQ 28546, were found in the culture broth of Chromobacterium violaceum.[3)]

Before the synthetic study of bulgecins, we first carried out the synthesis of dehydroxymethylbulgecin A (**5**) in which one component called bulgecinine, (2S,4S,5R)-4-hydroxy-5-hydroxymethylproline (**3**)[4)], was replaced with (2S,4S)-4-hydroxyproline, i.e., allo-4-hydroxy-L-proline (**4**)[5)]. As shown in Fig. 1, the oxazoline deivative **14** prepared from the protected N-acetylglucosamine was coupled with N-benzyloxycarbonyl-(2S,4S)-4-hydroxyproline methyl ester (**15**) in the presence of p-toluenesulfonic acid. The product **16** was saponified and converted into N-hydroxysuccinimide ester **17**. 4-Hydroxyl group in N-acetylglucosamine moiety of the compound **17** was then sulfated with DCC-H_2SO_4.[6)] The sulfate **18** neutralized with triethylamine was coupled with taurine. Finally all benzyl type protecting groups were removed by catalytic hydrogenation to give dehydroxymethylbulgecin A (**5**) which was prepared as disodium and monoacetic acid salts.[7)]

Interestingly, the synthetic analog **5** did not possess the ability of bulge formation any more. The fact clearly indicated that hydroxymethyl group in bulgecinine residue was quite important for the exhibition of characteristic biological activity in bulgecins. According to the present work, we could establish the synthetic route of bulgecins and are now engaging in the syntheses of bulgecins as well as several analogs for the elucidation on structure-activity relationship of these unique glycopeptides.



1 R=$NHCH_2CH_2SO_3H$
2 R=$NHCH_2CH_2COOH$



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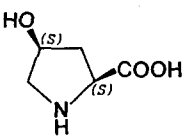

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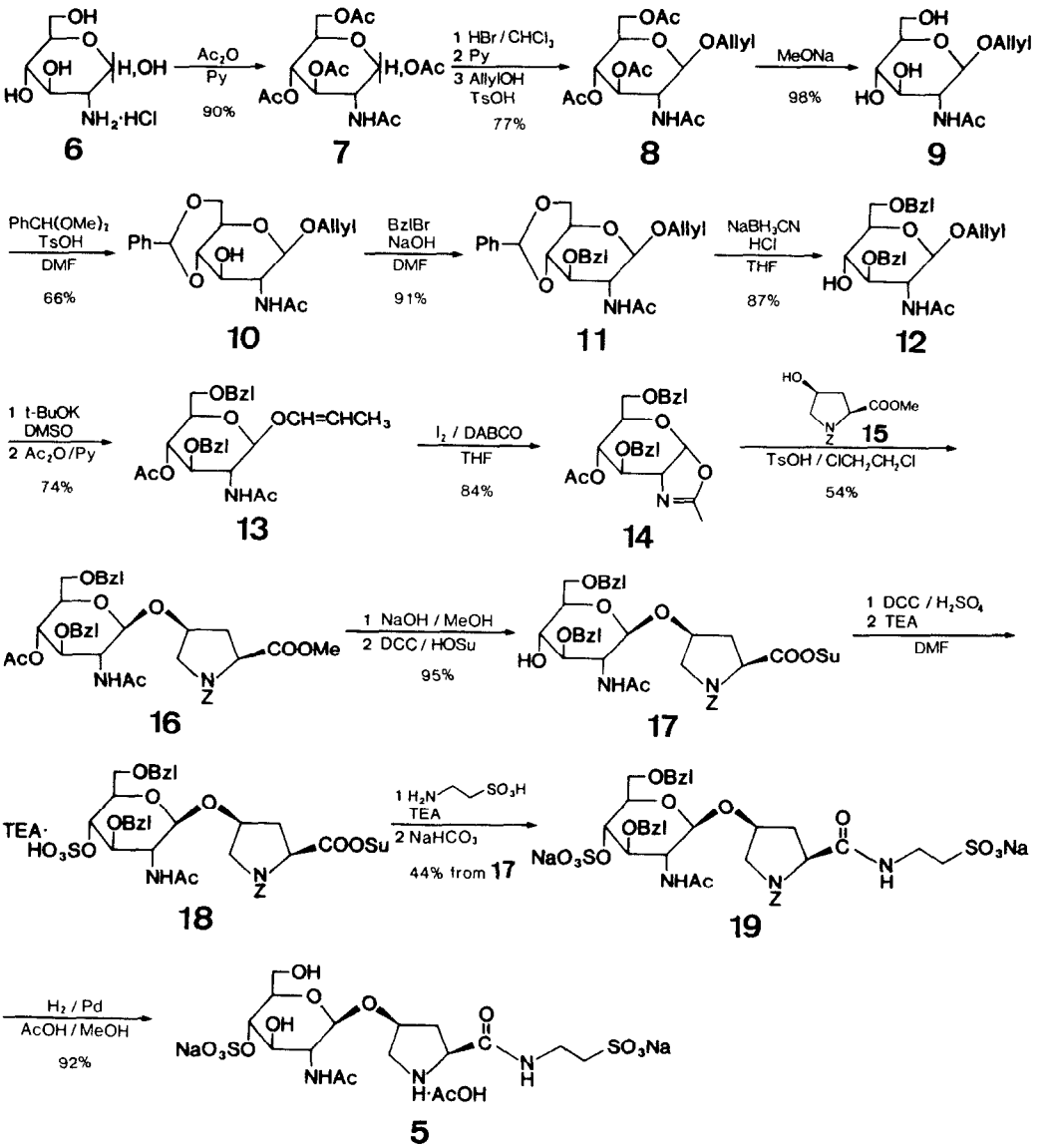

Fig. 1. Synthetic scheme of dehydroxymethylbulgecin A (5).

References and Notes

1. A part of this work was presented at 52nd National Meeting of the Chemical Society of Japan, Kyoto, April 1986, Abstr., No. 2N32.
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7. The structure of **5** was confirmed spectrometrically and by elemental analysis. Details of the spectral data as well as the physicochemical properties will be reported soon elsewhere.

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