SYNTHETIC APPROACH TO THE B-RING OF THE PEPTIDE ANTIBIOTIC NISIN

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The series of lanthionine containing peptidyl antibiotics (lantibiotics) has solicited much interest over the last few years. These lantibiotics includes nisin, subtilin, epidermin, gallidermin and pep-5.

Nisin (*Fig. 1*) is produced by strains of *Lactococcus lactis* and is active against Gram-positive bacteria as well as inhibiting sporulation of Bacilli and Clostridia (Hurst, 1981). The modified structure results from enzymatic maturation of a 57-residue prepropeptide *via* selective dehydration of serine and threonine residues followed by stereospecific cysteine-thiol addition to afford the thioether cyclic structures. The amino acid homologies between nisin and the other lantibiotics is high, being between 32 and 59% (Kellner et al, 1988).

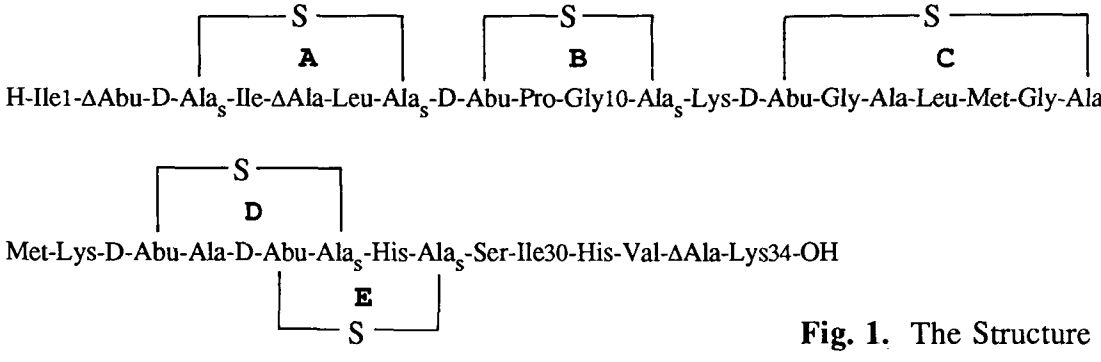

Fig. 1. The Structure of Nisin

It is clear that those regions which have been conserved are critical for activity; notable among these is the B-ring. Hence, it was decided to attempt a biomimetic synthesis of this ring which would also provide information on the role of the maturation enzyme/s. Synthesis of the hexapeptide Ala-Thr-Pro-Gly-Cys(Acm)-Ala (**1**) was readily achieved on a solid support using the Fmoc/continuous flow SPPS methodology. However, the Thr residue was found to be resistant to dehydration.

On the other hand, dehydration of the dipeptide Boc-Ala-Thr was readily accomplished, and it was found that 3-ethyl-1-(3-dimethylaminopropyl)-carbodiimide (EDCI) with CuCl at 25 C for 18 h, with the exclusion of light, gave exclusively the dehydro-dipeptide Boc-Ala-Δ^ZAbu. This subunit was incorporated to yield Boc-Ala-Δ^ZAbu-Pro-Gly-Cys(Acm)-Ala (**2**). Cyclisation of (**2**) requires the initial decapping of the cysteine Acm-protection to liberate the free thiol. Side-chain deprotection was thus accomplished by treatment of (**2**)-solid support with mercuric acetate. To date, cyclisation has not been achieved on the decapped-(**2**)-solid support using acid or base catalysis or in the presence of a radical initiator. It is clear that cyclisation does not occur spontaneously and is hoped that base catalysed Michael addition will afford the desired cyclic product.

Hurst, A. (1981) Adv. Appl. Microbiol. 27: 85 - 123
Kellner, R. et al (1988) Eur. J. Biochem. 177: 53 - 59